IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

PFIZER INC, PFIZER IRELAND PHARMACEUTICALS, WARNER-LAMBERT COMPANY, WARNER-LAMBERT COMPANY, LLC and WARNER-LAMBERT EXPORT, LTD. Plaintiffs, v. RANBAXY LABORATORIES LIMITED, RANBAXY PHARMACEUTICALS, INC and RANBAXY INC. Defendants.	)	Civil Action No. 08-

COMPLAINT

Pfizer Inc., Pfizer Ireland Pharmaceuticals, Warner-Lambert Company, Warner-Lambert Company, LLC and Warner-Lambert Export Limited, (collectively referred to as "Pfizer"), by their attorneys, for their complaint against Ranbaxy Laboratories Limited ("Ranbaxy Laboratories"), Ranbaxy Pharmaceuticals, Inc. ("Ranbaxy Pharmaceuticals") and Ranbaxy Inc. ("Ranbaxy Inc.")(collectively "Ranbaxy"), allege as follows:

1. This is an action by Pfizer against Ranbaxy for declaratory judgment of infringement of United States Letters Patent No. 6,087,511 ("the '511 patent) and United States Letters Patent No. 6,274,740 ("the '740 patent'). A copy of the '511 patent is attached hereto as Exhibit A. A copy of the '740 patent is attached hereto as Exhibit B.

2. On July 11, 2000 the United States Patent and Trademark Office issued the '511 patent, entitled "Process for the Production of Amorphous [R-(R*,R*)]-2-(4-Fluorophenyl)-β,δ-Dihydroxy-5-(1-Methylethyl)-3-Phenyl-4-[(Phenylamino)Carbonyl]-1H-Pyrrole-1-Heptanoic

Acid) Calcium Salt (2:1)", on an application filed by Min Lin, et al. and assigned to Warner-Lambert Company.

3. On August 14, 2001 the United States Patent and Trademark Office issued the '740 patent, entitled "Process for the Production of Amorphous [R-(R*,R*)]-2-(4-Fluorophenyl)-β,δ-Dihydroxy-5-(1-Methylethyl)-3-Phenyl-4-[(Phenylamino)Carbonyl]-1H-Pyrrole-1-Heptanoic Acid) Calcium Salt (2:1)", on an application filed by Lin Min, et al. and assigned to Warner-Lambert Company.

PARTIES, JURISDICTION AND VENUE

4. Pfizer Inc is a corporation organized and existing under the laws of the State of Delaware and has a place of business at 235 East 42nd Street, New York, New York 10017.

5. Warner-Lambert Company is a corporation formerly organized under the laws of the State of Delaware with offices for service of process at 235 East 42nd Street, New York, New York 10017. Warner-Lambert Company has been the owner of record of the '511 and the '740 patents since their issuance.

6. Warner-Lambert Company became a wholly owned subsidiary of Pfizer Inc effective June 19, 2000.

7. Warner-Lambert Company was converted into Warner-Lambert Company, LLC, a Delaware limited liability company by certificate dated December 31, 2002. Warner-Lambert Company, LLC has offices located at 235 East 42nd Street, New York, New York 10017.

8. Pfizer Ireland Pharmaceuticals is partnership organized and existing under the laws of Ireland, with registered offices at Pottery Road, Dun Laoghaire, Co. Dublin, Ireland. Pfizer Ireland Pharmaceuticals is a wholly owned, indirect subsidiary of Pfizer Inc.

9. Warner-Lambert Export, Ltd. is a corporation formerly organized under the laws of Ireland with a registered office located at Pottery Road, Dun Laoghaire, Co. Dublin, Ireland.

10. The exclusive licensee of the '511 patent is Pfizer Ireland Pharmaceuticals, formerly Warner-Lambert Export, Ltd.

11. The exclusive licensee of the '740 patent is Pfizer Ireland Pharmaceuticals, formerly Warner-Lambert Export, Ltd.

12. Pfizer, through Parke-Davis Pharmaceutical Research, a division of Warner-Lambert Company, holds an approved New Drug Application for an atorvastatin formulation which it sells under the registered name Lipitor®.

13. Upon information and belief, Ranbaxy Laboratories is a corporation organized and existing under the laws of India, with corporate offices located at 19, Nehru Place New Delhi - 110019 India.

14. Ranbaxy Inc. is a corporation organized and existing under the laws of the State of Delaware, and has a place of business located at 600 College Road East, Princeton, New Jersey 08540.

15. Upon information and belief, Ranbaxy Inc. was formerly known as Ranbaxy Pharmaceuticals Inc.

16. Upon information and belief, Ranbaxy Inc. is a wholly-owned subsidiary of Ranbaxy Laboratories.

17. Ranbaxy Pharmaceuticals, Inc. is a corporation organized and existing under the laws of the State of Delaware, and has a place of business located at 600 College Road East, Princeton, New Jersey 08540.

18. Upon information and belief, Ranbaxy Inc. and Ranbaxy Pharmaceuticals Inc. are the agents for Ranbaxy Laboratories.

19. This action arises under the Patent Laws of the United States, Title 35, United States Code. This Court has subject matter jurisdiction over this action pursuant to the provisions of Title 28, United States Code, Sections 1331 and 1338.

20. Upon information and belief, Ranbaxy Laboratories, Ranbaxy Pharmaceuticals and Ranbaxy Inc. are subject to personal jurisdiction in this District.

21. Venue is proper in this District pursuant to the provisions of Title 28, United States Code, Sections 1391(c), (d) and 1400(b).

FIRST CLAIM FOR RELIEF:
DECLARATORY JUDGMENT OF INFRINGEMENT OF THE '511 PATENT

22. Pfizer realleges paragraphs 1 through 21 above as if fully set forth herein.

23. This count arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202, based upon an actual controversy between the parties.

24. Pfizer has received a letter dated February 28, 2003 from Ranbaxy Pharmaceuticals (the "February 28, 2003 letter") which notified Pfizer that Ranbaxy Laboratories had filed an Abbreviated New Drug Application (ANDA), ANDA No. 76-477, seeking approval from FDA to engage in the commercial manufacture, use, and sale of a product containing atorvastatin as the active ingredient ("Ranbaxy's Atorvastatin Product") on a date which is prior to the expiration of the '511 patent. A copy of the February 28, 2003 letter is attached hereto as Exhibit C.

25. Ranbaxy has taken immediate and active steps to obtain FDA approval to sell in the United States and to commence sale in the United States of Ranbaxy's Atorvastatin Product immediately following FDA approval.

26. Pursuant to 35 U.S.C. § 271(e)(2) and (e)(4), Pfizer obtained a judgment which enjoins the effective date of approval of Ranbaxy's ANDA No. 76-477 until the date of

expiration of United States Letters Patent Nos. 4,681,893 ("the '893 patent") and its patent term extension (September 24, 2009, with attached six months of pediatric exclusivity ending on March 24, 2010, to which Pfizer is entitled).

27. The expiration date for the '511 patent is July 16, 2016.

28. The '511 patent covers a method of making amorphous atorvastatin.

29. Upon information and belief, Ranbaxy intends to import into the United States and/or to offer to sell, sell or use within the United States, all for purposes not exempt under 35 U.S.C. § 271(e)(1), Ranbaxy's Atorvastatin Product prior to the expiration of the '511 patent.

30. Upon information and belief, Ranbaxy's Atorvastatin Product is made or is intended to be made by a process which if practiced in the United States would infringe the '511 patent.

31. Upon information and belief, Ranbaxy's importation for purposes not exempt under 35 U.S.C. § 271(e)(1) into the United States and/or future offer to sell, sale or use for purposes not exempt under 35 U.S.C. § 271(e)(1) within the United States of Ranbaxy's Atorvastatin Product will infringe the '511 patent pursuant to 35 U.S.C. §271 (g).

32. Pfizer will be irreparably harmed if Ranbaxy is not enjoined from infringing the '511 patent.

SECOND CLAIM FOR RELIEF;
DECLARATORY JUDGMENT OF INFRINGEMENT OF THE '740 PATENT

33. Pfizer realleges paragraphs 1 through 32 above as if fully set forth herein.

34. This count arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202, based upon an actual controversy between the parties.

35. Pfizer has received a letter dated February 28, 2003 from Ranbaxy Pharmaceuticals (the "February 28, 2003 letter") which notified Pfizer that Ranbaxy

Laboratories had filed an Abbreviated New Drug Application (ANDA), ANDA No. 76-477, seeking approval from FDA to engage in the commercial manufacture, use, and sale of a product containing atorvastatin as the active ingredient ("Ranbaxy's Atorvastatin Product") on a date which is prior to the expiration of the '740 patent. A copy of the February 28, 2003 letter is attached hereto as Exhibit C.

36. Ranbaxy has taken immediate and active steps to obtain FDA approval to sell in the United States and to commence sale in the United States of Ranbaxy's Atorvastatin Product immediately following FDA approval.

37. Pursuant to 35 U.S.C. § 271(e)(2) and (e)(4), Pfizer obtained a judgment which enjoins the effective date of approval of Ranbaxy's ANDA No. 76-477 until the date of expiration of United States Letters Patent Nos. 4,681,893 ("the '893 patent") and its patent term extension (September 24, 2009, with attached six months of pediatric exclusivity ending on March 24, 2010, to which Pfizer is entitled).

38. The expiration date for the '740 patent is July 16, 2016.

39. The '740 patent covers a method of making amorphous atorvastatin.

40. Upon information and belief, Ranbaxy intends to import into the United States and/or to offer to sell, sell or use within the United States, all for purposes not exempt under 35 U.S.C. § 271(e)(1), Ranbaxy's Atorvastatin Product prior to the expiration of the '740 patent.

41. Upon information and belief, Ranbaxy's Atorvastatin Product is made or is intended to be made by a process which if practiced in the United States would infringe the '740 patent.

42. Upon information and belief, Ranbaxy's importation for purposes not exempt under 35 U.S.C. § 271(e)(1) and/or offer to sell, sale or use for purposes not exempt under 35

U.S.C. § 271(e)(1) within the United States of Ranbaxy's Atorvastatin Product will infringe the '740 patent pursuant to 35 U.S.C. §271 (g).

43. Pfizer will be irreparably harmed if Ranbaxy is not enjoined from infringing the '740 patent.

WHEREFORE, Pfizer requests the following relief:

A. A declaratory judgment that Ranbaxy's Atorvastatin Product is made by the use of the process claimed in the '511 patent and that its importation into the United States and its offer for sale, sale and/or use in the United States is an infringement of the '511 patent.

B. A declaratory judgment that Ranbaxy's Atorvastatin Product is made by the use of the process claimed in the '740 patent and that its importation into the United States and its offer for sale, sale and/or use in the United States is an infringement of the '740 patent.

C. A judgment permanently enjoining Ranbaxy, each of their officers, agents, servants, employees and attorneys, and those persons in active concert or participation with them or any of them, from making, using, selling, offering to sell, or importing the atorvastatin product described in Ranbaxy's ANDA 76-477 and made by the processes claimed in the '511 patent until July 16, 2016, the expiration date of the '511 patent.

D. A judgment permanently enjoining Ranbaxy, each of their officers, agents, servants, employees and attorneys, and those persons in active concert or participation with them or any of them, from making, using, selling, offering to sell, or importing the atorvastatin product described in Ranbaxy's ANDA 76-477

and made by the processes claimed in the '740 patent until July 16, 2016, the expiration date of the '740 patent.

E. Attorneys' fees in this action under 35 U.S.C. § 285;

F. Costs and expenses in this action; and

G. Such further and other relief as this Court may deem just and proper.

RESPECTFULLY SUBMITTED,

/s/Rudolf E. Hutz

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Exhibit "A"

US006087511A

United States Patent [19]

Lin et al.

[11] Patent Number: 6,087,511

[45] Date of Patent: Jul. 11, 2000

[54] **PROCESS FOR THE PRODUCTION OF AMORPHOUS [R-(R*,R*)]-2-(4-FLUOROPHENYL)-β,δ-DIHYDROXY-5-(1-METHYLETHYL)-3-PHENYL-4-[(PHENYLAMINO)CARBONYL]-1H-PYRROLE-1-HEPTANOIC ACID) CALCIUM SALT (2:1)**

[75] Inventors: **Min Lin**, Plainsboro, N.J.; **Dieter Schweiss**, Holland, Mich.

[73] Assignee: **Warner-Lambert Company**, Morris Plains, N.J.

[21] Appl. No.: **08/983,369**

[22] PCT Filed: **Jul. 16, 1996**

[86] PCT No.: **PCT/US96/11807**

§ 371 Date: **Jan. 15, 1998**

§ 102(e) Date: **Jan. 15, 1998**

[87] PCT Pub. No.: **WO97/03960**

PCT Pub. Date: **Feb. 6, 1997**

[51] **Int. Cl.**[7] **C07D 207/335**; C07D 207/34; A61K 31/40

[52] **U.S. Cl.** **548/537**; 514/422; 514/423; 514/429; 548/517

[58] **Field of Search** 548/517, 537; 514/422, 423

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,681,893	7/1987	Roth	514/422
5,003,080	3/1991	Butler et al.	548/517
5,097,045	3/1992	Butler et al.	549/373
5,103,024	4/1992	Millar et al.	549/373
5,124,482	6/1992	Butler et al.	564/169
5,149,837	9/1992	Butler et al.	549/333
5,155,251	10/1992	Butler et al.	558/442
5,216,174	6/1993	Butler et al.	548/517
5,245,047	9/1993	Butler et al.	548/517
5,248,793	9/1993	Millar et al.	548/375
5,273,995	12/1993	Roth	514/422
5,280,126	1/1994	Butler et al.	548/517
5,342,952	8/1994	Butler et al.	546/245
5,397,792	3/1995	Butler et al.	514/326
5,446,054	8/1995	Butler et al.	514/326
5,969,156	10/1999	Briggs et al.	548/537

FOREIGN PATENT DOCUMENTS

0247633	12/1987	European Pat. Off. .
0330172	8/1989	European Pat. Off. .
0409281	1/1991	European Pat. Off. .
89/07598	8/1989	WIPO .
94/20492	9/1994	WIPO .

OTHER PUBLICATIONS

Pharmaceutical Research, vol. 10, No. 10, 1993, pp. 1461–1465, Kearney, et al.

Baumann et al, Tetrahedron Letters, vol. 33, No. 17, pp. 2283–2284, 1992.

Konno, Chem. Pharm. Bull., vol. 38, No. 7, pp. 2003–2007, 1990.

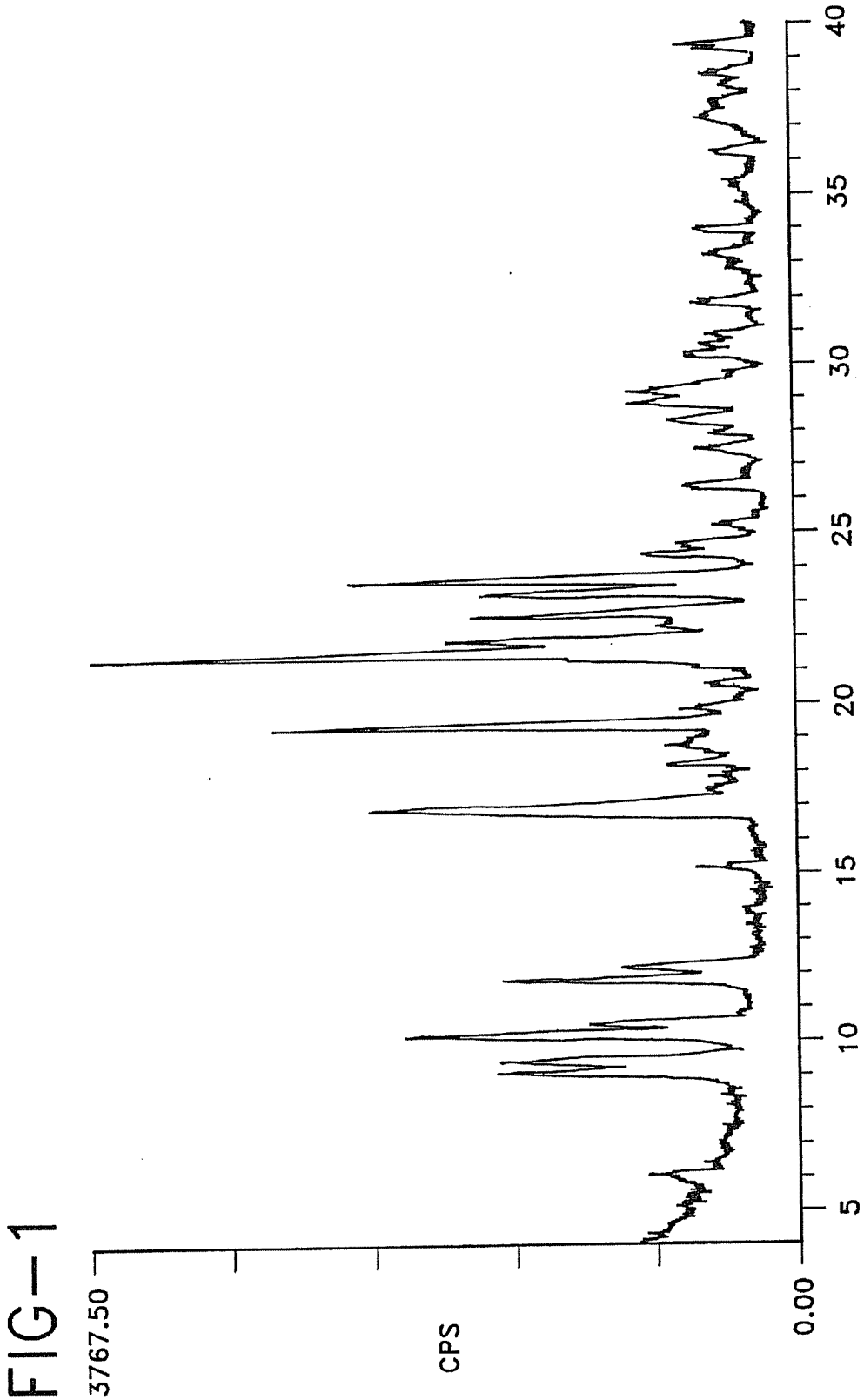
Primary Examiner—Floyd D. Higel

Attorney, Agent, or Firm—Francis J. Tinney

[57] **ABSTRACT**

A process for the preparation of amorphous atorvastatin is described where crystalline Form I atorvastatin is dissolved in a non-hydroxylic solvent and after removal of the solvent affords amorphous atorvastatin.

24 Claims, 3 Drawing Sheets



FIG—1

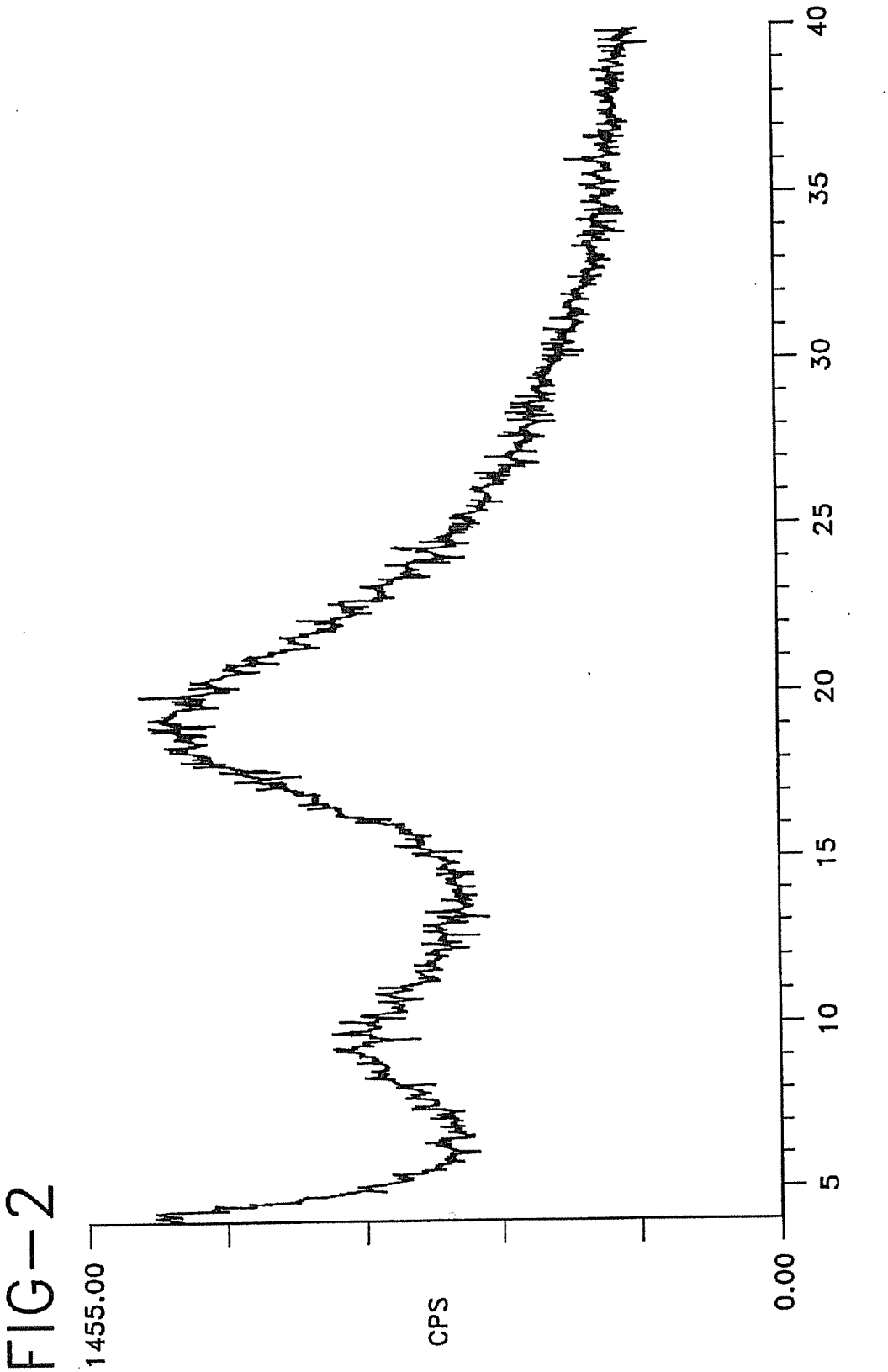
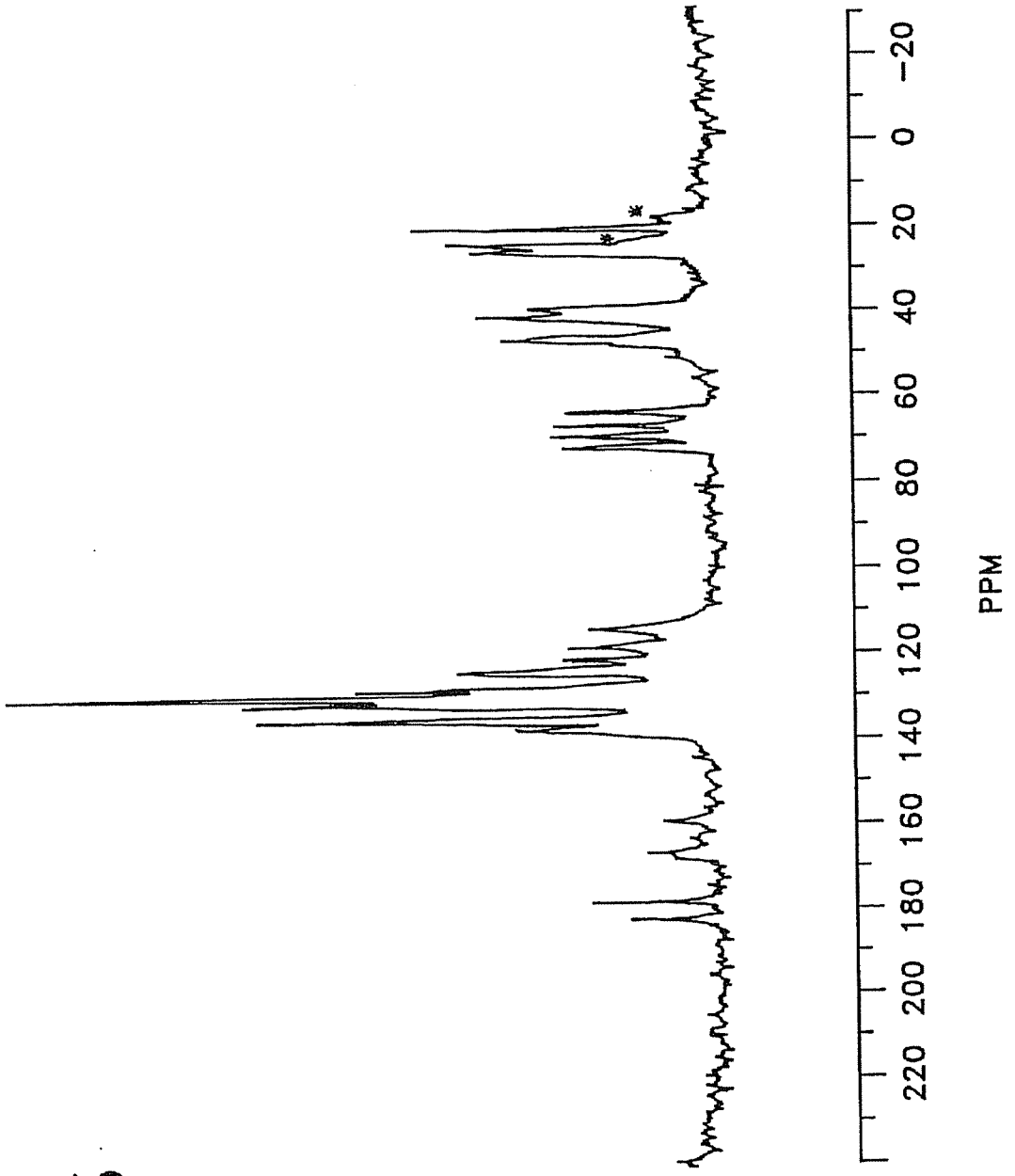


FIG-2



FIG−3

PROCESS FOR THE PRODUCTION OF AMORPHOUS [R-(R*,R*)] -2-(4-FLUOROPHENYL)-β,δ-DIHYDROXY-5-(1-METHYLETHYL)-3-PHENYL-4-[(PHENYLAMINO)CARBONYL]-1H-PYRROLE-1-HEPTANOIC ACID) CALCIUM SALT (2:1)

This application is a 371 of PCT/US/96/11807 filed Jul. 16, 1996.

BACKGROUND OF THE INVENTION

The present invention relates to a novel process for amorphous atorvastatin which is known by the chemical name [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt which is useful as a pharmaceutical agent. Atorvastatin is useful as an inhibitor of the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase) and is thus useful as a hypolipidemic and hypocholesterolemic agent.

U.S. Pat. No. 4,681,893, which is herein incorporated by reference, discloses certain trans-6-[2-(3- or 4-carboxamido-substituted-pyrrol-1-yl)alkyl]-4-hydroxy-pyran-2-ones including trans (±)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[(2-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide.

U.S. Pat. No. 5,273,995, which is herein incorporated by reference, discloses the enantiomer having the R form of the ring-opened acid of trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[(2-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide, i.e., [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid.

U.S. Pat. Nos. 5,003,080; 5,097,045; 5,103,024; 5,124,482; 5,149,837; 5,155,251; 5,216,174; 5,245,047; 5,248,793; 5,280,126; 5,397,792; and 5,342,952, which are herein incorporated by reference, disclose various processes and key intermediates for preparing atorvastatin.

Atorvastatin is prepared as its calcium salt, i.e., [R-(R*, R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1). The calcium salt is desirable since it enables atorvastatin to be conveniently formulated in, for example, tablets, capsules, lozenges, powders, and the like for oral administration.

Concurrently filed U.S. Patent Applications titled "Crystalline [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic Acid Calcium Salt (2:1)" and "Form III Crystalline [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic Acid Calcium Salt: (2:1)" commonly owned, attorney's Case Numbers PD-5250-01-FJT, Ser. No. 08/945,812, now U.S. Pat. No. 5,969,156, and PD-5333-01-FJT, Ser. No. 08/945,817, now abandoned, disclose atorvastatin in various new crystalline forms designated Form I, Form II, Form III, and Form IV.

Atorvastatin disclosed in the above United States Patents is an amorphous solid. We have found that after the advent of crystalline atorvastatin, the production of amorphous atorvastatin by the previously disclosed processes was not consistently reproducible.

It has been disclosed that the amorphous forms in a number of drugs exhibit different dissolution characteristics and in some cases different bioavailability patterns compared to the crystalline form (Konno T., *Chem. Pharm. Bull.*, 1990;38:2003–2007). For some therapeutic indications one bioavailability pattern may be favored over another. Therefore, it is desirable to have a procedure for converting the crystalline form of a drug to the amorphous form.

The object of the present invention is a process which is amenable to large-scale production for converting crystalline Form I atorvastatin into amorphous atorvastatin.

We have surprisingly and unexpectedly found that solutions of atorvastatin in a non-hydroxylic solvent afford, after removal of the solvent, amorphous atorvastatin.

SUMMARY OF THE INVENTION

Accordingly, the present invention is a novel process for the preparation of amorphous atorvastatin and hydrates thereof which comprises:

(a) dissolving crystalline Form I atorvastatin in a non-hydroxylic solvent; and

(b) removing the solvent to afford amorphous atorvastatin.

In a preferred embodiment of the invention, the non-hydroxylic solvent is selected from the group consisting of: tetrahydrofuran, and mixtures of tetrahydrofuran and toluene.

In another preferred embodiment of the invention, the solvent is removed in a vacuum dryer.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention is further described by the following non-limiting examples which refer to the accompanying FIGS. 1, 2, and 3, short particulars of which are given below.

FIG. 1 Diffractogram of Form I atorvastatin ground for 2 minutes (Y-axis=0 to maximum intensity of 3767.50 counts per second(cps))

FIG. 2 Diffractogram of amorphous atorvastatin (Y-axis=0 to maximum intensity of 1455.00 cps)

FIG. 3 Solid-state ^{13}C nuclear magnetic resonance spectrum with spinning side bands identified by an asterisk of Form I atorvastatin.

DETAILED DESCRIPTION OF THE INVENTION

Crystalline Form I atorvastatin may be characterized by its X-ray powder diffraction pattern and/or by its solid state nuclear magnetic resonance spectrum (NMR).

X-RAY POWDER DIFFRACTION

Amorphous and Form I Atorvastatin

Amorphous and Form I atorvastatin were characterized by their X-ray powder diffraction patterns. Thus, the X-ray diffraction patterns of amorphous and Form I atorvastatin were measured on a Siemens D-500 diffractometer with CuK_α radiation.

Equipment

Siemens D-500 Diffractometer-Kristalloflex with an IBM-compatible interface, software=DIFFRAC AT (SOCABIM 1986, 1992).

CuK_α radiation (20 mA, 40 kV, λ=1.5406 Å) Slits I and II at 1°) electronically filtered by the Kevex Psi Peltier Cooled Silicon [Si(Li)]Detector (Slits: III at 1° and IV at 0.15°).

Methodology

The silicon standard is run each day to check the X-ray tube alignment.

Continuous θ/2θ coupled scan: 4.00° to 40.00° in 2θ, scan rate of 6°/min: 0.4 sec/0.04° step (scan rate of 3°/min: 0.8 sec/0.04° step for amorphous atorvastatin).

Sample tapped out of vial and pressed onto zero-background quartz in aluminum holder. Sample width 13–15 mm (sample width ~16 mm for amorphous atorvastatin).

Samples are stored and run at room temperature.

Grinding

Grinding is used to minimize intensity variations for the diffractogram of Form I atorvastatin disclosed herein. However, if grinding significantly altered the diffractogram or increased the amorphous content of the sample, then the diffractogram of the unground sample was used.

Table 1 lists the 2θ, d-spacings, and relative intensities of all lines in the unground sample with a relative intensity of >20% for crystalline Form I atorvastatin. Table 1 also lists the relative intensities of the same lines in a diffractogram measured after 2 minutes of grinding. The intensities of the sample ground for 2 minutes are more representative of the diffraction pattern without preferred orientation. It should also be noted that the computer-generated, unrounded numbers are listed in this table.

TABLE 1

Intensities and Peak Locations of all Diffraction Lines With Relative Intensity Greater Than 20% for Form I Atorvastatin

2θ	d	Relative Intensity (>20%) No Grinding	Relative Intensity (>20%)* Ground 2 Minutes
9.150	9.6565	37.42	42.60
9.470	9.3311	46.81	41.94
10.266	8.6098	75.61	55.67
10.560	8.3705	24.03	29.33
11.853	7.4601	55.16	41.74
12.195	7.2518	20.03	24.62
17.075	5.1887	25.95	60.12
19.485	4.5520	89.93	73.59
21.626	4.1059	100.00	100.00
21.960	4.0442	58.64	49.44
22.748	3.9059	36.95	45.85
23.335	3.8088	31.76	44.72
23.734	3.7457	87.55	63.04
24.438	3.6394	23.14	21.10
28.915	3.0853	21.59	23.42
29.234	3.0524	20.45	23.36

*The second relative intensity column gives the relative intensities of the diffraction lines on the original diffractogram after 2 minutes of grinding.

SOLID STATE NUCLEAR MAGNETIC RESONANCE (NMR)

Methodology

All solid-state ^{13}C NMR measurements were made with a Bruker AX-250, 250 MHz NMR spectrometer. High resolution spectra were obtained using high-power proton decoupling and cross-polarization (CP) with magic-angle spinning (MAS) at approximately 5 kHz. The magic-angle was adjusted using the Br signal of KBr by detecting the side bands as described by Frye and Maciel (Frye J. S. and Maciel G. E., *J. Mag. Res.*, 1982;48:125). Approximately 300 to 450 mg of sample packed into a canister-design rotor was used for each experiment. Chemical shifts were referenced to external tetrakis (trimethylsilyl)silane (methyl signal at 3.50 ppm) (Muntean J. V. and Stock L. M., *J. Mag. Res.*, 1988;76:54).

Table 2 shows the solid-state spectrum for crystalline Form I atorvastatin.

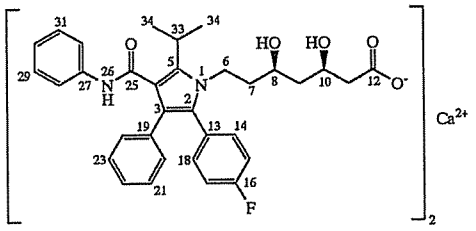


TABLE 2

Carbon Atom Assignment and Chemical Shift for Form I Atorvastatin

Assignment (7 kHz)	Chemical Shift
C12 or C25	182.8
C12 or C25	178.4
C16	166.7 (broad) and 159.3
Aromatic Carbons	
C2–C5, C13–C18, C19–C24, C27–C32	137.0, 134.9, 131.1, 129.5, 127.6, 123.5, 120.9, 118.2, 113.8
C8, C10	73.1, 70.5, 68.1, 64.9
Methylene Carbons	
C6, C7, C9, C11	47.4, 41.9, 40.2
C33	26.4, 25.2
C34	21.3

Amorphous atorvastatin of the present invention can exist in anhydrous forms as well as hydrated forms. In general, the hydrated forms, are equivalent to anhydrous forms and are intended to be encompassed within the scope of the present invention.

As previously described, amorphous atorvastatin is useful as an inhibitor of the enzyme, HMG-CoA reductase and is thus useful as a hypolipidemic and hypocholesterolemic agent.

The present invention provides a process for the commercial preparation of amorphous atorvastatin.

Thus, crystalline Form I atorvastatin is dissolved in a non-hydroxylic solvent such as, for example, tetrahydrofuran, mixtures of tetrahydrofuran and toluene and the like at a concentration of about 25% to about 40%. Preferably, crystalline Form I atorvastatin is dissolved in tetrahydrofuran at a concentration of about 25% to about 40% containing up to about 50% toluene as a co-solvent. The solvent is removed using, for example, drying technology such as, for example, vacuum drying, spray drying, and the like. Preferably, the drying procedure uses an agitated pan dryer such as, for example, Comber Turbodry Vertical Pan Dryer and the like. Drying initially is carried out at about 20° C. to about 40° C. and subsequently at about 70° C. to about 90° C. under vacuum at about 5 mm Hg to about

25 mm Hg for about 3 to about 5 days. Preferably, initial drying is carried out at about 35° C. and subsequently at about 85° C. at about 5 mm Hg to about 25 mm Hg for about 5 days. The initial solution dries to a brittle foam that is broken up by mechanical agitation to afford amorphous atorvastatin.

The following nonlimiting examples illustrate the inventors' preferred methods for preparing the compounds of the invention.

EXAMPLE 1

[R-(R*,R*)]-2-(4-Fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic Acid Hemi Calcium Salt (Form I Atorvastatin)

A mixture of (2R-trans)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide (atorvastatin lactone) (U.S. Pat. No. 5,273,995) (75 kg), methyl tertiary-butyl ether (MTBE) (308 kg), methanol (190 L) is reacted with an aqueous solution of sodium hydroxide (5.72 kg in 950 L) at 48–58° C. for 40 to 60 minutes to form the ring-opened sodium salt. After cooling to 25–35° C., the organic layer is discarded, and the aqueous layer is again extracted with MTBE (230 kg). The organic layer is discarded, and the MTBE saturated aqueous solution of the sodium salt is heated to 47–52° C. To this solution is added a solution of calcium acetate hemihydrate (11.94 kg) dissolved in water (410 L), over at least 30 minutes. The mixture is seeded with a slurry of crystalline Form I atorvastatin (1.1 kg in 11 L water and 5 L methanol) shortly after addition of the calcium acetate solution. The mixture is then heated to 51–57° C. for at least 10 minutes and then cooled to 15–40° C. The mixture is filtered, wished with a solution of water (300 L) and methanol (150 L) followed by water (450 L). The solid is dried at 60–70° C. under vacuum for 3 to 4 days to give crystalline Form I atorvastatin (72.2 kg).

EXAMPLE 2

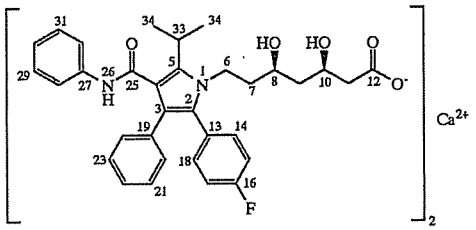
[R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic Acid Hemi Calcium Salt (Amorphous Atorvastatin)

Crystalline Form I atorvastatin (Example 1) (30 kg) is dissolved with agitation in tetrahydrofuran (75 L) at ambient temperature under a nitrogen atmosphere. Toluene (49.4 L) is added slowly once solution is achieved. The solution is then transferred through a 0.45 micron Pall filter to a 200 L Comber Turbodry Vertical Pan Dryer. The transfer system is rinsed to the dryer with additional tetrahydrofuran (4.5 L). Full vacuum is applied, and the solution is concentrated at 35° C. with mild agitation. Near the end of the concentration process, the agitator is lifted. The product turns into a brittle glassy foam. The agitator is gradually lowered, breaking the brittle foam into a free flowing powder. The powder is agitated and the temperature is raised to 85° C. under vacuum (6 to 8 mm Hg) to lessen the residual solvent levels. After 4 days of drying, the desired residual solvent levels of 0.01% tetrahydrofuran and 0.29% toluene are achieved. The free flowing white powder (27.2 kg) is unloaded from the dryer. The product is amorphous by X-ray powder diffraction.

We claim:

1. A process for the preparation of amorphous atorvastatin or hydrates thereof which comprises:

(a) dissolving crystalline Form I atorvastatin having the formula



in a non-hydroxylic solvent; and

(b) removing the solvent by drying to afford said amorphous atorvastatin or hydrates thereof.

2. A process according to claim 1 wherein the non-hydroxylic solvent in Step (a) is selected from the group consisting of: tetrahydrofuran, and mixtures of tetrahydrofuran and toluene.

3. A process according to claim 2 wherein the solvent is a mixture of tetrahydrofuran and toluene.

4. A process according to claim 1 wherein the solvent in Step (b) is removed by vacuum drying or spray drying.

5. A process according to claim 4 wherein the solvent in Step (b) is removed by vacuum drying.

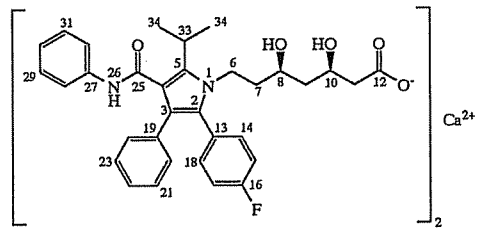
6. A process according to claim 5 wherein vacuum drying is initially carried out at about 20° C. to about 40° C. and subsequently at about 70° C. to about 90° C. under vacuum at about 5 mm Hg to about 25 mm Hg.

7. A process according to claim 6 wherein vacuum drying is initially carried out at about 35° C. and subsequently at about 85° C. under vacuum at about 5 mm Hg to about 25 mm Hg.

8. A process according to claim 5 wherein the material obtained after drying is a brittle foam which is broken up by mechanical agitation.

9. A process for the preparation of anhydrous amorphous atorvastatin which comprises:

(a) dissolving crystalline Form I atorvastatin having the formula



in a non-hydroxylic solvent; and

(b) removing the solvent by drying to afford said anhydrous amorphous atorvastatin.

10. A process according to claim 9 wherein the non-hydroxylic solvent in Step (a) is selected from the group consisting of: tetrahydrofuran, and mixtures of tetrahydrofuran and toluene.

11. A process according to claim 10 wherein the solvent is a mixture of tetrahydrofuran and toluene.

12. A process according to claim 9 wherein the solvent in Step (b) is removed by vacuum drying or spray drying.

13. A process according to claim 12 wherein the solvent in Step (b) is removed by vacuum drying.

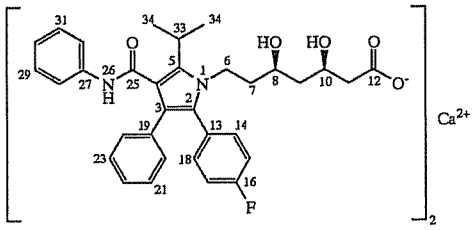
14. A process according to claim **13** wherein vacuum drying is initially carried out at about 20° C. to about 40° C. and subsequently at about 70° C. to about 90° C. under vacuum at about 5 mm Hg to about 25 mm Hg.

15. A process according to claim **14** wherein vacuum drying is initially carried out at about 35° C. and subsequently at about 85° C. under vacuum at about 5 mm Hg to about 25 mm Hg.

16. A process according to claim **13** wherein the material obtained after drying is a brittle foam which is broken up by mechanical agitation.

17. A process for the preparation of hydrated amorphous atorvastatin which comprises:

(a) dissolving crystalline Form I atorvastatin having the formula



in a non-hydroxylic solvent; and

(b) removing the solvent by drying to afford said hydrated amorphous atorvastatin.

18. A process according to claim **17** wherein the non-hydroxylic solvent in Step (a) is selected from the group consisting of: tetrahydrofuran, and mixtures of tetrahydrofuran and toluene.

19. A process according to claim **18** wherein the solvent is a mixture of tetrahydrofuran and toluene.

20. A process according to claim **17** wherein the solvent in Step (b) is removed by vacuum drying or spray drying.

21. A process according to claim **20** wherein the solvent in Step (b) is removed by vacuum drying.

22. A process according to claim **21** wherein vacuum drying is initially carried out at about 20° C. to about 40° C. and subsequently at about 70° C. to about 90° C. under vacuum at about 5 mm Hg to about 25 mm Hg.

23. A process according to claim **22** wherein vacuum drying is initially carried out at about 35° C. and subsequently at about 85° C. under vacuum at about 5 mm Hg to about 25 mm Hg.

24. A process according to claim **21** wherein the material obtained after drying is a brittle foam which is broken up by mechanical agitation.

* * * * *

Exhibit "B"

US006274740B1

(12) **United States Patent**
Lin et al.

(10) **Patent No.: US 6,274,740 B1**
(45) **Date of Patent: Aug. 14, 2001**

(54) **PROCESS FOR THE PRODUCTION OF AMORPHOUS [R-(R*,R*)]-2-(4-FLUOROPHENYL)-β, δ-DIHYDROXY-5-(1-METHYLETHY)-3-PHENYL-4-[(PHENYLAMINO) CARBONYL]-1H-PYRROLE-1-HEPTANOIC ACID CALCIUM SALT (2:1)**

(75) Inventors: **Min Lin**, Plainsboro, NJ (US); **Dieter Schweiss**, Holland, MI (US)

(73) Assignee: **Warner-Lambert Company**, Morris Plains, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/657,469**

(22) Filed: **Sep. 7, 2000**

Related U.S. Application Data

(62) Continuation of application No. 09/453,189, filed on Dec. 2, 1999, now abandoned, which is a continuation of application No. 08/983,369, filed as application No. PCT/US96/11807 on Jul. 16, 1996, now Pat. No. 6,087,511

(60) Provisional application No. 60/001,453, filed on Jul. 17, 1995.

(51) **Int. Cl.**[7] **C07D 207/335**; C07D 207/34

(52) **U.S. Cl.** **548/537**

(58) **Field of Search** 548/537

(56) **References Cited**

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4,681,893	7/1987	Roth	514/422
5,003,080	3/1991	Butler et al.	548/517
5,097,045	3/1992	Butler et al.	549/373
5,103,024	4/1992	Millar et al.	549/373
5,124,482	6/1992	Butler et al.	564/169
5,149,837	9/1992	Butler et al.	549/333
5,155,251	10/1992	Butler et al.	558/442
5,216,174	6/1993	Butler et al.	548/517
5,245,047	9/1993	Butler et al.	548/517
5,248,793	9/1993	Millar et al.	548/375
5,273,995	12/1993	Roth	514/422
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Baumann, et al., *Tetrahedron Letters*, vol. 33, No. 17, pp. 2283–2284, 1992.

Konno, *Chem. Pharm. Bull.*, vol. 38, No. 7, pp. 2003–2007, 1990.

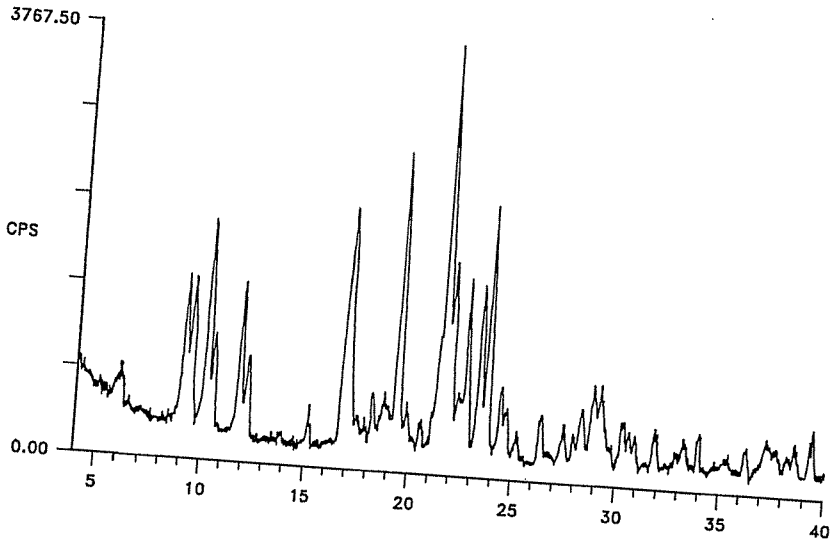
Pharmaceutical Research, vol. 10, No. 10, 1993, pp 1461–1465, Kearney, et al.

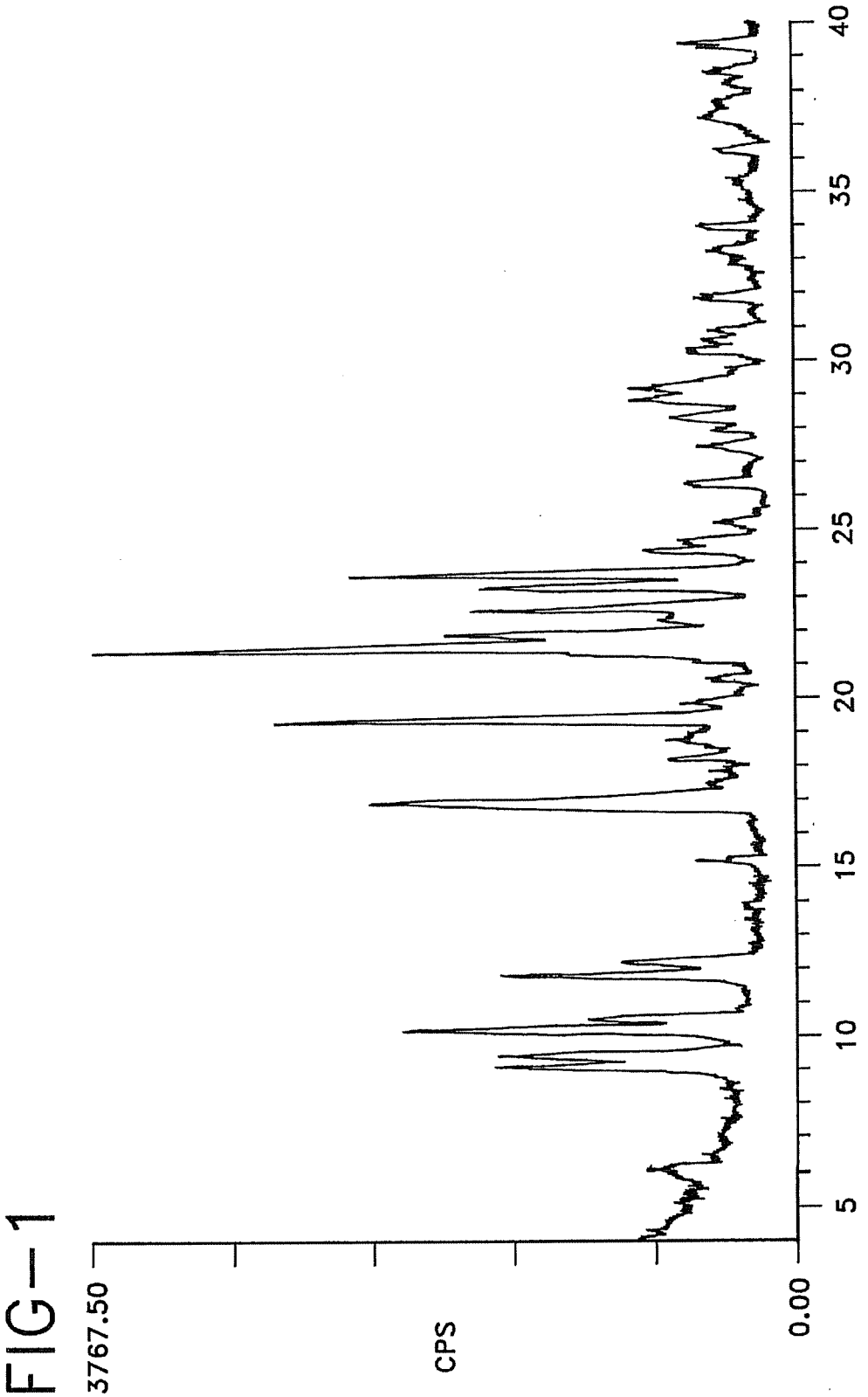
Primary Examiner—Jane C. Oswecki
(74) *Attorney, Agent, or Firm*—Francis J. Tinney

(57) **ABSTRACT**

A novel process for the preparation of amorphous atorvastatin is described where crystalline Form I atorvastatin is dissolved in a non-hydroxylic solvent and after removal of the solvent affords amorphous atorvastatin.

3 Claims, 3 Drawing Sheets





FIG—1

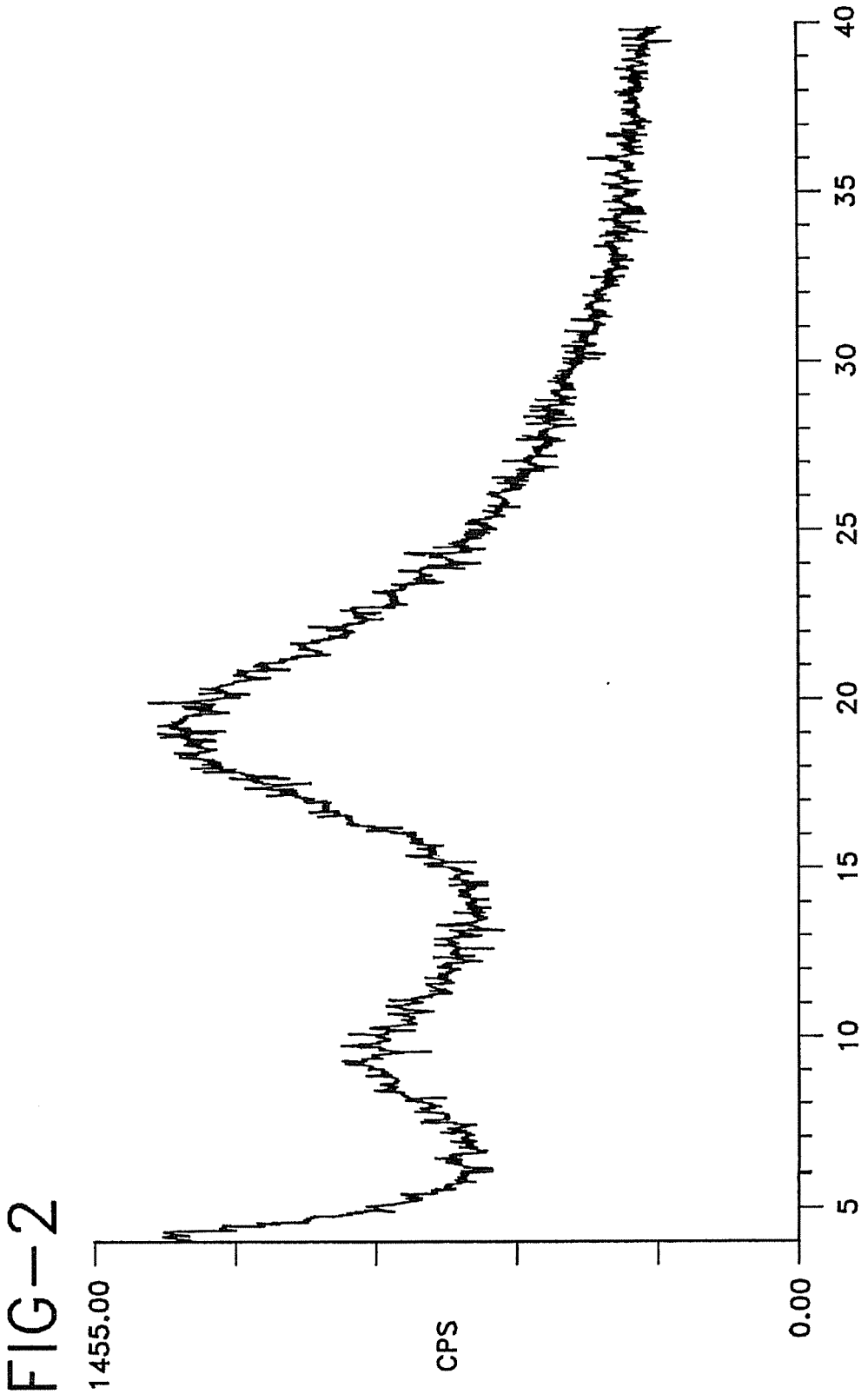
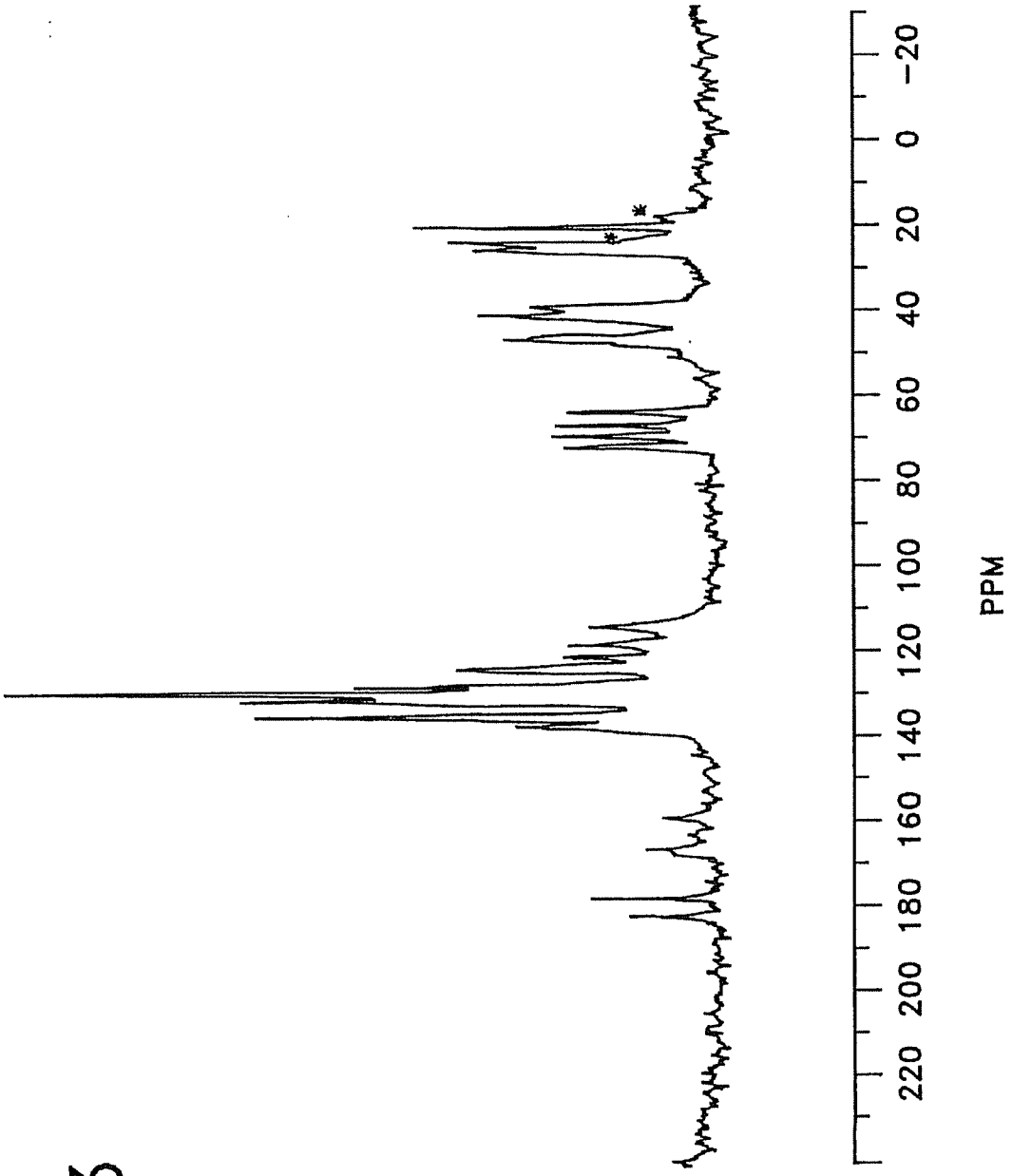


FIG-2



FIG−3

PROCESS FOR THE PRODUCTION OF AMORPHOUS [R-(R*,R*)]-2-(4-FLUOROPHENYL)-β, δ-DIHYDROXY-5-(1-METHYLETHY)-3-PHENYL-4-[(PHENYLAMINO) CARBONYL]-1H-PYRROLE-1-HEPTANOIC ACID CALCIUM SALT (2:1)

This application is a continuation of U.S. Ser. No. 09/453,189 filed Dec. 2, 1999, abandoned, which is a continuation of U.S. Ser. No. 08/983,369 filed Jan. 15, 1998, now U.S. Pat. No. 6,087,511 issued Jul. 11, 2000, which is a §371 filing from PCT/US96/11807 filed Jul. 16, 1996, which claims priority from U.S. provisional application No. 60/001,453 filed Jul. 17, 1995.

BACKGROUND OF THE INVENTION

The present invention relates to a novel process for amorphous atorvastatin which is known by the chemical name [R—(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt which is useful as a pharmaceutical agent. Atorvastatin is useful as an inhibitor of the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-COA reductase) and is thus useful as a hypolipidemic and hypocholesterolemic agent.

U.S. Pat. No. 4,681,893, which is herein incorporated by reference, discloses certain trans-6-[2-(3- or 4-carboxamido-substituted-pyrrol-1- yl)alkyl]-4-hydroxy-pyran-2-ones including trans (±)-5- (4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[(2-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide.

U.S. Pat. No. 5,273,995, which is herein incorporated by reference, discloses the enantiomer having the R form of the ring-opened acid of trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[(2-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide, i.e., [R—(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid.

U.S. Pat. Nos. 5,003,080; 5,097,045; 5,103,024; 5,124,482; 5,149,837; 5,155,251; 5,216,174; 5,245,047; 5,248,793; 5,280,126; 5,397,792; and 5,342,952, which are herein incorporated by reference, disclose various processes and key intermediates for preparing atorvastatin.

Atorvastatin is prepared as its calcium salt, i.e., [R—(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1). The calcium salt is desirable since it enables atorvastatin to be conveniently formulated in, for example, tablets, capsules, lozenges, powders, and the like for oral administration.

Concurrently filed U.S. patent applications titled "Crystalline [R—(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic Acid Calcium Salt (2:1)"and" Form III Crystalline [R—(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic Acid Calcium Salt (2:1)" commonly owned, Ser. No. 08/945,812 now U.S. Pat. No. 5,969,156, and, Ser. No. 08/945,817, abandoned, disclose atorvastatin in various new crystalline forms designated Form I, Form II, Form III, and Form IV.

Atorvastatin disclosed in the above United States Patents is an amorphous solid. We have found that after the advent of crystalline atorvastatin, the production of amorphous atorvastatin by the previously disclosed processes was not consistently reproducible.

It has been disclosed that the amorphous forms in a number of drugs exhibit different dissolution characteristics and in some cases different bioavailability patterns compared to the crystalline form (Konno T., *Chem. Pharm. Bull.*, 1990;38:2003–2007). For some therapeutic indications one bioavailability pattern may be favored over another. Therefore, it is desirable to have a procedure for converting the crystalline form of a drug to the amorphous form.

The object of the present invention is a process which is amenable to large-scale production for converting crystalline Form I atorvastatin into amorphous atorvastatin.

We have surprisingly and unexpectedly found that solutions of atorvastatin in a non-hydroxylic solvent afford, after removal of the solvent, amorphous atorvastatin.

SUMMARY OF THE INVENTION

Accordingly, the present invention is a novel process for the preparation of amorphous atorvastatin and hydrates thereof which comprises:

(a) dissolving crystalline Form I atorvastatin in a non-hydroxylic solvent; and

(b) removing the solvent to afford amorphous atorvastatin.

In a preferred embodiment of the invention, the non-hydroxylic solvent is selected from the group consisting of: tetrahydrofuran, and mixtures of tetrahydrofuran and toluene.

In another preferred embodiment of the invention, the solvent is removed in a vacuum dryer.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention is further described by the following non-limiting examples which refer to the accompanying FIGS. **1**, **2**, and **3**, short particulars of which are given below.

FIG. **1** Diffractogram of Form I atorvastatin ground for 2 minutes (Y-axis=0 to maximum intensity of 3767.50 counts per second(cps)).

FIG. **2** Diffractogram of amorphous atorvastatin (Y-axis=0 to maximum intensity of 1455.00 cps).

FIG. **3** Solid-state ^{13}C nuclear magnetic resonance spectrum with spinning side bands identified by an asterisk of Form I atorvastatin.

DETAILED DESCRIPTION OF THE INVENTION

Crystalline Form I atorvastatin may be characterized by its X-ray powder diffraction pattern and/or by its solid state nuclear magnetic resonance spectrum (NMR).

X-ray Powder Diffraction

Amorphous and Form I Atorvastatin

Amorphous and Form I atorvastatin were characterized by their X-ray powder diffraction patterns. Thus, the X-ray diffraction patterns of amorphous and Form I atorvastatin were measured on a Siemens D-500 diffractometer with CuK_α radiation.

Equipment

Siemens D-500 Diffractometer-Kristalloflex with an IBM-compatible interface, software=DIFFRAC AT (SOCABIM 1986, 1992).

CuK_α radiation (20 mA, 40 kV, λ=1.5406 Å) Slits I and II at 1°) electronically filtered by the Kevex Psi Peltier Cooled Silicon [Si(Li)]Detector (Slits: III at 1° and IV at 0.15°).

Methodology

The silicon standard is run each day to check the X-ray tube alignment.

Continuous θ/2θcoupled scan: 4.00° to 40.00° in 2θ, scan rate of 6° /min: 0.4 sec/0.04° step (scan rate of 3°/min: 0.8 sec/0.04° step for amorphous atorvastatin).

Sample tapped out of vial and pressed onto zero-background quartz in aluminum holder. Sample width 13–15 mm (sample width ~16 mm for amorphous atorvastatin).

Samples are stored and run at room temperature.

Grinding

Grinding is used to minimize intensity variations for the diffractogram of Form I atorvastatin disclosed herein. However, if grinding significantly altered the diffractogram or increased the amorphous content of the sample, then the diffractogram of the unground sample was used.

Table 1 lists the 2θ, d-spacings, and relative intensities of all lines in the unground sample with a relative intensity of >20% for crystalline Form I atorvastatin. Table 1 also lists the relative intensities of the same lines in a diffractogram measured after 2 minutes of grinding. The intensities of the sample ground for 2 minutes are more representative of the diffraction pattern without preferred orientation. It should also be noted that the computer-generated, unrounded numbers are listed in this table.

TABLE 1

Intensities and Peak Locations of all Diffraction Lines With Relative Intensity Greater Then 20% for Form I Atorvastatin

2θ	d	Relative Intensity (>20%) No Grinding	Relative Intensity (>20%)* Ground 2 Minutes
9.150	9.6565	37.42	42.60
9.470	9.3311	46.81	41.94
10.266	8.6098	75.61	55.67
10.560	8.3705	24.03	29.33
11.853	7.4601	55.16	41.74
12.195	7.2518	20.03	24.62
17.075	5.1887	25.95	60.12
19.485	4.5520	89.93	73.59
21.626	4.1059	100.00	100.00
21.960	4.0442	58.64	49.44
22.748	3.9059	36.95	45.85
23.335	3.8088	31.76	44.72
23.734	3.7457	87.55	63.04
24.438	3.6394	23.14	21.10
28.915	3.0853	21.59	23.42
29.234	3.0524	20.45	23.36

*The second relative intensity column gives the relative intensities of the diffraction lines on the original diffractogram after 2 minutes of grinding.

Solid State Nuclear Magnetic Resonance (NMR) Methodology

All solid-state ^{13}C NMR measurements were made with a Bruker AX-250, 250 MHz NMR spectrometer. High resolution spectra were obtained using high-power proton decoupling and cross-polarization (CP) with magic-angle spinning (MAS) at approximately 5 kHz. The magic-angle was adjusted using the Br signal of KBr by detecting the side bands as described by Frye and Maciel (Frye J. S. and Maciel G. E., *J. Mag. Res.*, 1982;48:125). Approximately 300 to 450 mg of sample packed into a canister-design rotor was used for each experiment. Chemical shifts were referenced to external tetrakis (trimethylsilyl)silane (methyl signal at 3.50 ppm) (Muntean J. V. and Stock L. M., *J. Mag. Res.*, 1988;76:54).

Table 2 shows the solid-state spectrum for crystalline Form I atorvastatin.

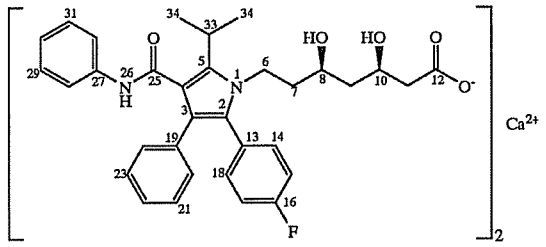


TABLE 2

Carbon Atom Assignment and Chemical Shift for Form I Atovastatin

Assignment (7 kHz)	Chemical Shift
C12 or C25	182.8
C12 or C25	178.4
C16	166.7 (broad) and 159.3
Aromatic Carbons	137.0
C2–C5, C13–C18, C129–C24, C27–C32	134.9
	131.1
	129.5
	127.6
	123.5
	120.9
	118.2
	113.8
C8, C10	73.1
	70.5
	68.1
	64.9
Methylene Carbons	47.4
C6, C7, C9, C11	41.9
	40.2
C33	26.4
	25.2
C34	21.3

Amorphous atorvastatin of the present invention can exist in anhydrous forms as well as hydrated forms. In general, the hydrated forms, are equivalent to anhydrous forms and are intended to be encompassed within the scope of the present invention.

As previously described, amorphous atorvastatin is useful as an inhibitor of the enzyme, HMG-CoA reductase and is thus useful as a hypolipidemic and hypocholesterolemic agent.

The present invention provides a process for the commercial preparation of amorphous atorvastatin.

Thus, crystalline Form I atorvastatin is dissolved in a non-hydroxylic solvent such as, for example, tetrahydrofuran, mixtures of tetrahydrofuran and toluene and the like at a concentration of about 25% to about 40%. Preferably, crystalline Form I atorvastatin is dissolved in tetrahydrofuran at a concentration of about 25% to about 40% containing up to about 50% toluene as a co-solvent. The solvent is removed using, for example, drying technology such as, for example, vacuum drying, spray drying, and the like. Preferably, the drying procedure uses an agitated pan dryer such as, for example, Comber Turbodry Vertical Pan Dryer and the like. Drying initially is carried out at about 20° C. to about 40° C. and subsequently at about 70° C. to about 90° C. under vacuum at about 5 mm Hg to about 25 mm Hg for about 3 to about 5 days. Preferably, initial drying is carried out at about 35° C. and subsequently at

about 85° C. at about 5 mm Hg to about 25 mm Hg for about 5 days. The initial solution dries to a brittle foam that is broken up by mechanical agitation to afford amorphous atorvastatin.

The following nonlimiting examples illustrate the inventors' preferred methods for preparing the compounds of the invention.

EXAMPLE 1

[R—(R*,R*)]-2-(4-Fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt (Form I Atorvastatin)

A mixture of (2R-trans)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide (atorvastatin lactone) (U.S. Pat. No. 5,273,995) (75 kg), methyl tertiary-butyl ether (MTBE) (308 kg), methanol (190 L) is reacted with an aqueous solution of sodium hydroxide (5.72 kg in 950 L) at 48–58° C. for 40 to 60 minutes to form the ring-opened sodium salt. After cooling to 25–35° C., the organic layer is discarded, and the aqueous layer is again extracted with MTBE (230 kg). The organic layer is discarded, and the MTBE saturated aqueous solution of the sodium salt is heated to 47–52° C. To this solution is added a solution of calcium acetate hemihydrate (11.94 kg) dissolved in water (410 L), over at least 30 minutes. The mixture is seeded with a slurry of crystalline Form I atorvastatin (1.1 kg in 11 L water and 5 L methanol) shortly after addition of the calcium acetate solution. The mixture is then heated to 51–57° C. for at least 10 minutes and then cooled to 15–40° C. The mixture is filtered, washed with a solution of water (300 L) and methanol (150 L) followed by water (450 L). The solid is dried at 60–70° C. under vacuum for 3 to 4 days to give crystalline Form I atorvastatin (72.2 kg).

EXAMPLE 2

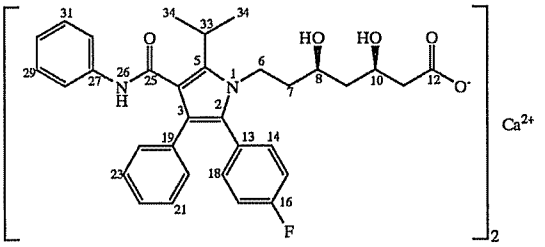
[R—(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt (Amorphous Atorvastatin)

Crystalline Form I atorvastatin (Example 1) (30 kg) is dissolved with agitation in tetrahydrofuran (75 L) at ambient temperature under a nitrogen atmosphere. Toluene (49.4 L) is added slowly once solution is achieved. The solution is then transferred through a 0.45 micron Pall filter to a 200 L Comber Turbodry Vertical Pan Dryer. The transfer system is rinsed to the dryer with additional tetrahydrofuran (4.5 L). Full vacuum is applied, and the solution is concentrated at 35° C. with mild agitation. Near the end of the concentration process, the agitator is lifted. The product turns into a brittle glassy foam. The agitator is gradually lowered, breaking the brittle foam into a free flowing powder. The powder is agitated and the temperature is raised to 85° C. under vacuum (6 to 8 mm Hg) to lessen the residual solvent levels. After 4 days of drying, the desired residual solvent levels of 0.01% tetrahydrofuran and 0.29% toluene are achieved. The free flowing white powder (27.2 kg) is unloaded from the dryer. The product is amorphous by X-ray powder diffraction.

What is claimed is:

1. A process for the preparation of amorphous atorvastatin or hydrates thereof which comprises:

(a) dissolving crystalline Form I atorvastatin having the formula

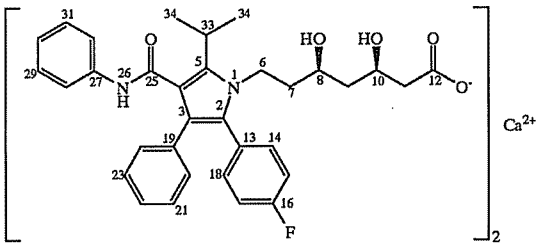


in a non-hydroxylic solvent at a concentration of about 25% to about 40%; and

(b) removing the solvent by drying to afford said amorphous atorvastatin or hydrates thereof.

2. A process for the preparation of anhydrous amorphous atorvastatin which comprises:

(a) dissolving crystalline Form I atorvastatin having the formula

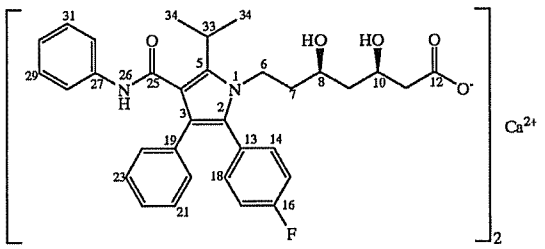


in a non-hydroxylic solvent at a concentration of about 25% to about 40%; and

(b) removing the solvent by drying to afford said anhydrous amorphous atorvastatin.

3. A process for the preparation of hydrated amorphous atorvastatin which comprises:

(a) dissolving crystalline Form I atorvastatin having the formula



in a non-hydroxylic solvent at a concentration of about 25% to about 40%; and

(b) removing the solvent by drying to afford said hydrated amorphous atorvastatin.

* * * * *

Exhibit "C"

RANBAXY

PHARMACEUTICALS INC.

Phone: (609) 720-5608 • Fax (609) 514-9779

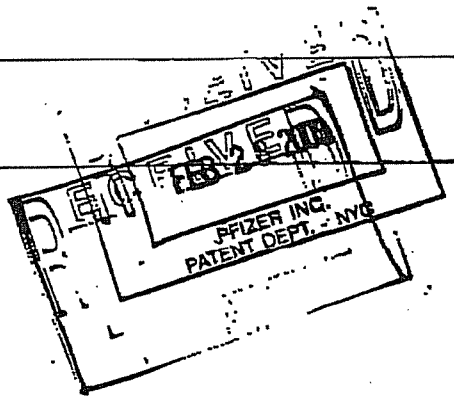
FAX

DATE: February 28, 2003

#OF PAGES: 23
(INCLUDING THIS COVER)

TO: Dr. Peter Richardson
Pfizer, Inc.
FAX NO.: (212) 573-1939

FROM: Jay R. Deshmukh, Esq.



RE: **Atorvastatin**
ANDA No. 76-477
U.S. Patent No. 5,273,995

Please see attached.

Jay R. Deshmukh, Esq.
Vice President - Intellectual Property

RANBAXY
PHARMACEUTICALS INC.

February 28, 2003

VIA FACSIMILE (212) 573-1939

CONFIRMATION VIA CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Dr. Peter Richardson
Senior Assistant General Counsel
and General Patent Counsel
Pfizer, Inc.
Legal Division
150 East 42nd Street, 5th Floor
New York, NY 10017-5755

Re: ATORVASTATIN
ANDA NO: 76-477
U.S. PATENT NO.: 5,273,995

Dear Dr. Richardson:

Pursuant to Section 505(j)(2)(B) of the Food, Drug and Cosmetic Act ("FDCA") and 21 C.F.R. 314.95, you are hereby notified as follows:

(1) Ranbaxy Laboratories Limited ("RLL") has previously submitted and the FDA has received an abbreviated new drug application ("ANDA") under FDCA Section 505(j)(2)(B)(ii) which contains bioavailability or bioequivalence data in order to obtain approval to engage in the commercial manufacture, use or sale of a drug product containing atorvastatin.

(2) RLL's ANDA referred to in paragraph (1) has been assigned No. 76-477.

(3) The established name for the drug product is atorvastatin, and the name of the drug product as listed on page 3-37 of the 22nd edition of the FDA publication entitled *Approved Drug Products With Therapeutic Equivalence Evaluations (2002)* (the "Orange Book") is Lipitor®, equivalent to 10 mg, 20 mg, 40 mg and 80 mg of atorvastatin.

(4) RLL's proposed drug product is in the form of tablets, which contain the equivalent of 10 mg, 20 mg, 40 mg and 80 mg of atorvastatin as the active ingredient.

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(5) On November 4, 2002, RLL sent a paragraph IV letter to Pfizer (received by Pfizer on November 6, 2002, per the return postcard) for ANDA 76-477 with respect to U.S. Patent Nos. 5,686,104; 5,969,156; and 6,126,971. On January 23, 2003 and on February 28, 2003, RLL sent paragraph IV letters to Pfizer for ANDA 76-477 with respect to the extension term and the unextended term of U.S. Patent No. 4,681,893, respectively.

(6) RLL has already amended its paragraph III certification in respect to U.S. Patent No. 5,273,995 ("the '995 Patent") to a paragraph IV certification. This letter will describe the factual and legal basis for this paragraph IV certification. Broadly speaking, no valid claim of the '995 patent will be infringed by the manufacture, use, sale, or offer to sell of the drug product for which ANDA No. 76-477 has been submitted.

The '995 Patent

U.S. Patent No. 5,273,995 ("the '995 patent") entitled "[R-(R*R*)]-2-(4-FLUOROPHENYL)-β,δ-DIHYDROXYL-5-(1-METHYLETHYL-3-PHENYL-4-[(PHENYLAMINO)CARBONYL]-1H-PYRROLE-1-HEPTANOIC ACID, ITS LACTONE FORM AND SALTS THEREOF" issued on December 28, 1993 to the inventor named on the '893 patent, Bruce D. Roth. The '995 Patent issued from U.S. Application Serial No. 07/660,976 ("the '976 Application"), filed February 26, 1991. The '976 application was filed as a continuation of U.S. Application Serial No. 07/384,187 ("the '187 Application), filed July 21, 1989, abandoned. The '995 Patent was assigned to Warner-Lambert.

The '995 patent contains a total of 12 claims, of which Claim 1 is independent, reciting the title enantiomerically specific compound, the lactone thereof, and pharmaceutically acceptable salts thereof. Claims 2-10 are directly or indirectly dependent from Claim 1. Claim 11 refers to Claim 1 and recites a pharmaceutical composition of the compounds of the '995 Patent. Claim 12 refers to Claim 1 and recites a method of inhibiting cholesterol synthesis using these compounds.

The Claims of the '995 patent

The claims are set forth below.

1. [R-(R*R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)-carbonyl]-1H-pyrrole-1-heptanoic acid or

(2R-trans)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide; or

pharmaceutically acceptable salts thereof.[1]

[1] Claim 1 has been rewritten from the block format as issued for clarity.

2. A compound of claim 1 which is [R-(R*R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)-carbonyl]-1H-pyrrole-1-heptanoic acid.

3. A compound of claim 1 which is (2R-trans)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide.

4. The monosodium salt of the compound of claim 2.

5. The monopotassium salt of the compound of claim 2.

6. The hemicalcium salt of the compound of claim 2.

7. The N-methylglucamine salt of the compound of claim 2.

8. The hemimagnesium salt of the compound of claim 2.

9. The hemizinc salt of the compound of claim 2.

10. The 1-deoxy-1-(methylamino)-D-glucitol mixture with the compound of claim 2.

11. A pharmaceutical composition for treating hypercholesterolemia comprising a hypocholesterolemic effective amount of a compound of claim 1 and a pharmaceutically acceptable carrier.

12. A method of inhibiting cholesterol synthesis in a human suffering from hypercholesterolemia comprising administering a compound of claim 1 in unit dosage form.

The Written Description of the '995 patent

The '995 Patent states that "the present invention provides for compounds consisting of [R-(R*R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)-carbonyl]-1H-pyrrole-1-heptanoic acid (compound of formula I), pharmaceutically acceptable salts thereof and (2R-trans)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide (the lactone form of the heptanoic acid or compound of formula II" (The '995 Patent, col. 2, lines 29-38). The '995 Patent also states that this R-enantiomer "provides surprising inhibition of the biosynthesis of cholesterol." (*Id.*, at 1:23-25).

The specification discloses that "[g]enerally, the compounds I and II of the present invention can be prepared by (1) resolving the racemate, that is prepared by the processes described in U.S. Pat. No. 4,681,893 ("the '893 Patent") which is incorporated by reference therefore, or (2) synthesizing the desired chiral form beginning from starting materials which are known or readily prepared using processes analogous to those which are known." (The '995 Patent, col. 4, lines 7-14). The resolution is described in Scheme I and Examples 6 and 7 of the '995 Patent. (*Id.* at 4:15–6:36, 13:34–14:28). The asymmetric synthesis is described in Scheme 2 and Examples 1–5. (*Id.* at 6:37–7:60, 9:40–13:32). As pointed out in the patent, "the 'trans racemate' of Scheme I means a mixture of ... [the] [R(R*R*)] isomer and [S(R*R*)] isomer." (*Id.*, at 5:35-36, and 6:33).

Furthermore, the '995 Patent provides IC_{50} values, allegedly based on the CSI test disclosed in the '893 Patent, for the R-form enantiomer (0.0044 $\mu mol \cdot L^{-1}$), the S-form enantiomer (0.44 $\mu mol \cdot L^{-1}$), and the racemate of atorvastatin (0.045 $\mu mol \cdot L^{-1}$). (*See Id.*, at 7:65 – col. 9, line 7.

The Prosecution History of the '995 patent

The parent application of the '995 Patent, the '187 Application, was filed July 21, 1989, and included no claim to foreign or domestic priority. (*See* Prosecution History of the '995 patent, Paper 1 (July 21, 1989)). The Power of Attorney executed by Roth names ten attorneys; five of these attorneys were also named as attorneys for the '893 Patent. The signing attorney was Jerry F. Janssen of Warner-Lambert Co., 2800 Plymouth Road, Ann Arbor, MI 48105.

An Information Disclosure Statement was filed by the applicant, listing the following three references:

- U.S. Pat. No. 4,681,893 (the '893 Patent);
- Stokker, et al.; J. Med. Chem., vol. 28, pp. 347-358 (1985); and
- Tetrahedron Letters, vol. 28, no. 13, pp. 1385-1388 (1987).

Only these three references appear on the face of the patent, and there is no indication from any other portion of the prosecution history of the '995 Patent that any other references were discussed or considered by either the applicant or the Examiner.

The '187 Application was filed with 12 claims, set forth below.

1. [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-((1-methylethyl)-3-phenyl-4-[(phenylamino)-carbonyl]-1H-pyrrole-1-heptanoic acid or (2R-trans)-5-(4-fluorophenyl)-2-(1-methylethyl-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide; and pharmaceutically acceptable salts thereof.

2. A compound of claim 1 which is [R-(R*R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-((1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid.

3. A compound of claim 1 which is (2R-trans)-5-(4-fluorophenyl)-2-(1-methylethyl-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide.

4. The monosodium salt of the compound of claim 2.

5. The monopotassium salt of the compound of claim 2.

6. The hemicalcium salt of the compound of claim 2.

7. The N-methylglucamine salt of the compound of claim 2.

8. The hemimagnesium salt of the compound of claim 2.

9. The hemizinc salt of the compound of claim 2.

10. The 1-deoxy-1-(methylamino)-D-glucitol mixture with the compound of claim 2.

11. A pharmaceutical composition for treating hypercholesterolemia comprising a hypocholesterolemic effective amount of a compound of claim 1 and a pharmaceutically acceptable carrier.

12. A method of inhibiting cholesterol synthesis in a human suffering from hypercholesterolemia comprising administering a compound of claim 1 in unit dosage form.

Among other rejections, all claims were rejected under 35 U.S.C. § 102(b) as anticipated by the '893 Patent. ('995 Patent, Prosecution History, Paper 3, "Examiner's Action," March 22, 1990).

In a response filed on August 6, 1990, the Applicant argued that the 35 U.S.C. § 102(b) rejection over the '893 Patent was inappropriate because the '893 Patent teaches only the racemic mixtures of compounds whereas the claimed compounds are enantiomerically pure.[2] Specifically, the Applicant argued that "each isomer of [the '893 Patent] *is* a mixture of enantiomers and not the currently claimed individual enantiomers having an R chirality."

[2] The Applicant appears to have used the term "racemic" and the phrase "mixture of enantiomers" interchangeably in prosecuting the '995 Patent.

(emphasis added). The Applicant continued, arguing that the '893 Patent disclosure was "*limited* to a mixture of enantiomers."[3] (emphasis added).

In the second (and Final) Office Action mailed on November 13, 1990, the Examiner again rejected all claims as anticipated by the '893 Patent, applying the rule of *In re Schaumann*, 197 U.S.P.Q. 5 (C.C.P.A. 1978), wherein a limited genus of similar compounds may anticipate a species. Specifically, the examiner asserted that the specific enantiomer now claimed was one of a genus of four disclosed in the '893 Patent.

The Applicant continued prosecution by filing a File Wrapper Continuation application on February 26, 1991, to which serial number 07/660,976 was assigned. Therein, the Applicant argued that the 35 U.S.C. § 102(b) rejection was improper because (1) the genus/species analysis of *Schaumann* did not apply when comparing racemic mixtures and optically pure isomers, and (2) under *In re Williams*, 36 C.C.P.A. 756, 171 F.2d 319 (1948), prior art disclosure of a racemate does not anticipate a purified enantiomer. Finally, the Applicant submitted a declaration by Bruce D. Roth, the sole inventor named on both the '893 and '995 Patents, which the Applicant stated was being provided to overcome any potential rejection under 35 U.S.C. § 103 ("the Roth Declaration"). The Roth Declaration reported that IC_{50} for atorvastatin calcium, its R-enantiomer, and the racemate in the CSI screen were 0.025, > 1.00, and 0.26 $\mu mol \cdot L^{-1}$, respectively.

In the first Office Action (made final) under the continued prosecution, mailed September 23, 1991, the Examiner again rejected all claims under 35 U.S.C. § 102(b) as anticipated by the '893 Patent. In support of the rejection, the Examiner pointed out the following paragraph from the '893 Patent, found sufficient to sustain the 35 U.S.C. § 102(b) rejection:

> The compounds of structural formula I above possess two asymmetric carbon centers, one at the 4-hydroxy position of the pyran-2-one ring, and the other at the 6-position of the pyran-2-one ring where the alkylpyrrole group is attached. This asymmetry gives rise to four possible isomers, two of which are the R-cis- and S-cis-isomers and the other two of which are the R-trans- and S-trans-isomers. This invention contemplates only the trans- form of the compounds of formula I above.

---

[3] Similarly, during the prosecution of its corresponding European patent application, Warner-Lambert argued: "[W]hat is described in [the '893 Patent] is the *racemate* [sic.] of compounds, wherein both chiral centers have the same configuration.... [T]here is no teaching whatsoever, how a person skilled in the art could make the pure optical isomers separately." *Response to European Patent Office* (June 20, 1995) at pg. 2 (emphasis added). Warner-Lambert later reemphasized and expanded on this argument, stating: "There is no teaching whatsoever in [the '893 Patent] that the racemate can *actually* be split and in practice it needed extensive research to find a feasible method for separating the individual enantiomers." *Response to European Patent Office in Preparation for Oral Proceedings* (June 10, 1996) at pg. 3. (emphasis added) Based on Warner-Lambert's arguments, the European Examiner later observed that "only the racemate is disclosed in the closest prior art." *Decision to Refuse a European Patent Application* (Sept. 5, 1996) at pg. 4.

The '995 Patent at 3:45–54.[4]

The Applicant's attorney personally interviewed the Examiner on November 4, 1991 and the Examiner maintained the 35 U.S.C. § 102(b) rejection.

The Applicant appealed to the Board of Patent Appeals and Interferences ("the Board") on December 20, 1991. In its Appeal Brief, the Applicant's position was that the '893 Patent did not anticipate the appealed claims, arguing that the specification of the '893 Patent teaches the existence of four isomers (two diastereomers and their enantiomers) and identifies the preferred diastereomeric pair of compounds (the "trans" diastereomer of the lactone). The Applicant argued that the '893 Patent does not teach which of the enantiomers of the "trans" diastereomer is preferred or how to synthesize either pure enantiomer. The Applicant further argued that although the '893 Patent suggested the existence of the enantiomers, it did not enable one of ordinary skill to practice the invention claimed in the '995 Patent, because the '893 Patent does not teach one how to separate the enantiomers, or how to determine which is preferred. Finally, the Applicant argued that under *Williams*, disclosure of a racemate does not anticipate a claim to a purified enantiomer.

After an oral hearing on August 11, 1992, the Board reversed the 35 U.S.C. § 102(b) rejection, concluding that the appealed claims were directed to "the *R* isomer which is essentially free of any of the *S* isomer also present in the trans racemate."[5] The Board agreed with the Applicant that the '893 Patent, "at best, only describes the trans racemate containing the R-trans and the S-trans isomers in admixture. Nowhere does Roth [the '893 Patent] state or suggest which optical isomer is preferred and, moreover, does not specifically mention how one skilled in the art could make the pure optical isomer separately." Following *Williams*, the Board affirmed that disclosure of a racemate does not anticipate claim to a purified enantiomer However, the Board specifically recommended that the Examiner analyze the claims under 35 U.S.C. § 103. Despite this recommendation and without making a 35 U.S.C. § 103 rejection, the Examiner mailed the Notice of Allowability on July 6, 1993. The '995 Patent issued on December 28, 1993.

The Unambiguous Meaning of the Claims of the '995 Patent

The specific chemical names and stereochemical designations recited in Claim 1 of the '995 Patent signify that the claims of the '995 Patent refer to only one enantiomer of the "so-called "trans" form racemic mixture of the ring-opened heptanoic acid/lactone atorvastatin. Specifically, the claims of the '995 Patent refer to the R-trans enantiomer. Although the claims of the '995 Patent do not recite any limitation with regard to purity, the Board of Appeals unambiguously concluded that appealed claims were directed to "the *R* isomer which is

---

[4] The Examiner mistakenly cited this passage as 4:45–54.

[5] The Board did not elaborate on the meaning of the phrase "essentially free."

essentially free of any of the *S* isomer also present in the trans racemate." A court would also read this "purity" limitation into the claims of the '995 Patent, since the claims of the '995 Patent would have been found to be unpatentable as anticipated by the disclosure of the '893 Patent if those claims were not read to include such a "purity" limitation.

Since dependent claims 2-10 implicitly incorporate all limitations of claim 1 by depending from claim 1, and independent claims 11 and 12 expressly incorporate all limitations of claim 1 by reference to claim 1, all claims in the '995 Patent will be read by a court to require the R-trans enantiomer. *See* 35 U.S.C. § 112, ¶ 4.

The Claims of the '995 Patent Are Invalid

A. The Relevant Law of Patent Invalidity

Each claim of an issued patent is presumed to be valid, 35 U.S.C. § 282 (1994), and this presumption can only be overcome in a subsequent court challenge by facts supported by clear and convincing evidence. *See, e.g., WMS Gaming Inc. v. Int'l Game Techs.*, 184 F.3d 1339, 1355 (Fed. Cir. 1999). Although the presumption of validity is unvarying, the burden of proving invalidity may be more easily met where the challenge is based on prior art or legal argument that is "more pertinent than that considered by the Patent and Trademark Office (PTO)." *Ryco, Inc. v. Ag-Bag Corp.*, 857 F.2d 1418, 1423 (Fed. Cir. 1988).

Obviousness is a question of law based on underlying facts. *In re Geiger*, 815 F.2d 686, 688 (Fed. Cir. 1987). The trier of fact determines: (1) the scope and content of the prior art, (2) the differences between the prior art and the claims at issue, (3) the level of ordinary skill in the art, and (4) the existence of objective indicia of non-obviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). The statute requires that obviousness be determined "at the time the invention was made." The patent may not be used as a template for selecting and combining prior art references. *Union Carbide Corp. v. American Can Co.*, 724 F.2d 1567, 1576 n.6 (Fed. Cir. 1984).

Because the patentee has acknowledged that the prior art '893 Patent discloses, at least, the trans-form racemic mixture of atorvastatin and the '995 Patent claims a single, purified enantiomer of this form of atorvastatin, case law applying the laws of validity in the context of inventions involving the purification or resolution of racemic mixtures is relevant.

The case of *In re Williams*, 171 F.2d 319 (C.C.P.A. 1948), cited and applied during the prosecution of the '995 Patent, represents the latest of such decisions rendered prior to the enactment of the current Patent Act in 1952. In *Williams* the Court of Customs and Patent Appeals *revised* a Patent Office decision rejecting claims to the laevo rotatory form of a particular lactone "substantially free from the dextro rotatory form." *Id.* at 319. The court concluded that the claim recited novel subject matter because "[t]he existence of a compound as an ingredient of another substance does not negative novelty in a claim to the pure compound although it may, of course, render the claim unpatentable for lack of invention." *Id.* at 320. Furthermore, the court found the claimed invention patentable on the record before it because:

> There is no evidence of record to show actual knowledge of the racemic nature of the [prior art] product prior to April 3, 1939, when appellant's original application was filed....The record contains nothing to support a holding that those skilled in the art should have known that the [prior art] product was racemic, ...and it would not be proper to presume such knowledge.

Id. at 320.

A subsequent decision of the Court of Customs and Patent Appeals, *In re Adamson*, 275, F.2d 952 (C.C.P.A. 1960), clarifies the precedential effect of *In re Williams*. The *Adamson* court affirmed a Patent Office rejection of claims directed to a "*laevo*-isomer of a compound . . . and their acid addition salts and quaternary ammonium salts substantially separated from the *dextro*-isomer." *Id.* at 952. The court concluded that *Williams* "was not controlling in appellants' favor" for the following reasons:

> Appellants contend that their invention lies in the discoveries that the racemate of the [primary prior art] references can be separated, that the optical isomers exist, and that the laevo-isomer exhibits surprisingly superior spasmolytic activity, surprising because the prior art, it is alleged, would suggest that the dextro- and laevo-isomers would have substantially the same therapeutic activities. Finally appellants rely heavily upon the Williams case, which case, it is argued, requires a judgment in their favor.
>
> It is our opinion that the claimed compounds are unpatentable over either of the cited [primary] references in view of [the secondary reference]. Appellants do not dispute the facts that racemic mixtures of their isomers and acid addition salts are structurally disclosed in the primary references, that they are the product of organic syntheses, and that they have asymmetric carbon atoms. [The secondary reference] states that synthetically produced organic compounds containing an asymmetric carbon atom are racemic, i.e., optically inactive mixtures of equal amounts of the dextro- and laevo-isomers. In view of the teachings of [the secondary reference] we feel that one of ordinary skill in the stereoisomer and pharmaceutical arts would recognize that the [primary reference] compounds exist as racemates, hence the fact that no reference to stereoisomerism is made by the [primary] references themselves is of no moment.
>
> It is at this point that *In re Williams*, *supra*, is distinguishable. In that case the court held a laevo-isomer to be patentable over a reference showing the compound's formula. In so doing the court said it found nothing in the record on appeal to indicate that one skilled in the art "should have known that the Monatschefte [prior art] product was racemic" and concluded that it would have been improper to "presume such knowledge." The deficiency existing in the Williams record has been satisfied in the case at bar in the form of Karrer which

> clearly shows that one of ordinary skill in the art should have known that the Adamson compounds were racemic.

Id. at 954. The *Adamson* court also concluded that this bare knowledge that the racemate existed, in combination with a generalized method of separating the enantiomers of other, chemically-similar racemates provided ample motivation to separate the racemate of the primary reference. *Id.* at 954-955.

Finally, the *Adamson* court also considered a declaration alleging that the purified enantiomer exhibited unexpected results when compared to the racemate. The *Adamson* court explained that this allegation was not sufficient:

> The only other arguments submitted by appellants all relate to the laevo-isomer's superior spasmolytic activity, and are based primarily upon the showing of the White affidavit summarized earlier in this opinion. That affidavit shows the laevo-isomer to be about twice as active as the racemate, and the dextro-isomer to be virtually inactive, as antispasmodics. [The secondary reference] teaches that the pharmacological activity of two stereoisomers may differ substantially because of the nature of the substances with which they react to produce their physiological effects. Appellants argue that the compounds from which [the secondary reference] deduces that general principle are so different from their own laevo-isomers that the general rule is inapplicable here.
>
> Concededly those compounds are different. However, we find no reason of record to believe that [the secondary reference] statement would not teach one of ordinary skill in the art that the optical isomers of the [prior art] racemates, and the quaternary ammonium salts and acid addition salts thereof, may have different spasmolytic activities. In establishing that fact experimentally appellants have done no more than is suggested by the prior art and have ascertained no more than what would be expected by one skilled in the art, i.e., the activities are different. *The toxicity of the racemate is shown by the affidavit to lie between that of its isomers, which fact appears to us to be particularly expected.* We find that the contentions based upon the properties of the claimed compounds are devoid of persuasive force upon the issue of those compounds' obviousness.

Id. at 955. (emphasis added).

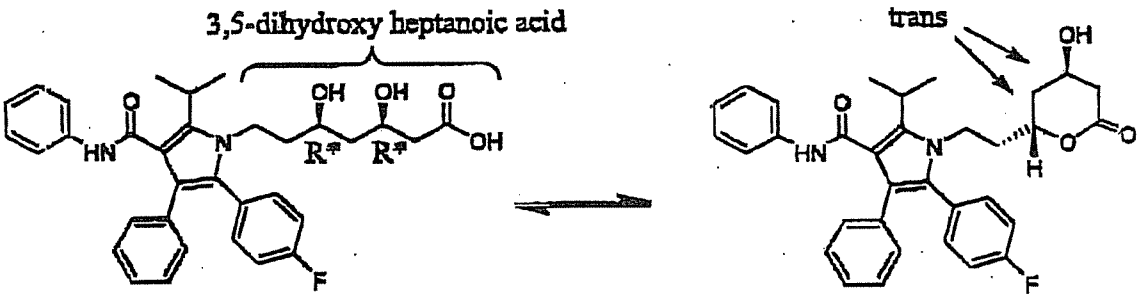
Accordingly, *In re Williams* "must be regarded as superseded by the later case of *In re Adamson, wherein the record was more complete on the subject of stereoisomerism.*" *Ex parte Openshaw*, 143 USPQ 40, 41 (Bd. Pat. App. 1964) (emphasis added).

B. The Relevant Prior Art

1. United States Patent No. 4,681,893 – The '893 Patent

U.S. Patent No. 4,681,893 ("the '893 patent") issued on July 21, 1987 and thus is prior art to the '995 patent under 35 U.S.C. §102(b); it was published more than one year prior to July 21, 1989, the earliest date to which the '995 Patent could conceivably claim domestic priority.

The '893 patent is directed to certain trans-6-[2-(3- or 4-carboxamido-substituted pyrrol-1-yl)alkyl]-4-hydroxypyran-2-ones, and discloses examples of such compounds in Table 1 at columns 7-10. The first compound in Table 1 is a lactone derivative having the chemical name trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide, the preparation of which is described in Example 1 at columns 10-13. As described at col. 13, lines 50-59, this lactone is readily formed from the corresponding ring-opened heptanoic acid as shown below:

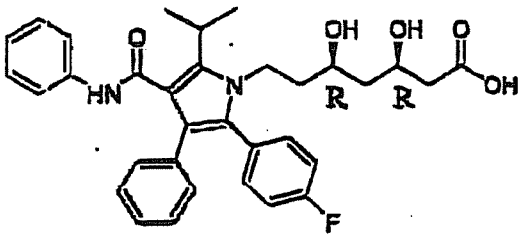


Ring-opened heptanoic acid form Lactone form

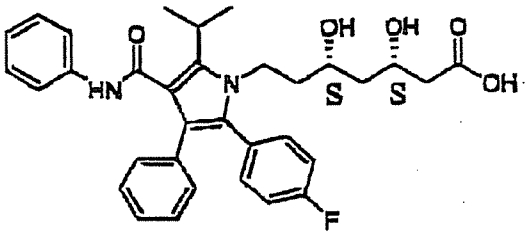
There term "trans" in the chemical name provided above refers to the stereochemical configuration of the lactone, in which the hydroxyl group on the lactone ring is on the opposite side of the lactone ring from the remainder of the molecule as shown above. The '893 Patent is directed to both the "trans" form lactones and the corresponding ring-opened hydroxy-acid forms of the disclosed compounds. *See* column 2, lines 39-43. The ring-opened hydroxy-acid form consists of a 3,5-dihydroxy heptanoic acid group that is attached to the remainder of the molecule. The Background section of the '893 Patent discloses that structurally related 3,5-dihydroxy-3-methylpentanoic acid derivatives (and the corresponding lactones) are known to inhibit the synthesis of cholesterol. *See* col. 1, lines 33-39. The lactone form is typically in equilibrium with the corresponding acid form, as indicated by the pair of opposing arrows shown above. Both the lactones and the corresponding ring-opened hydroxy-acids are therefore known to be potent inhibitors of cholesterol biosynthesis. *See* '893 Patent, col. 1, lines 63-67.

Example 1 of the '893 Patent reports a preparation of the (R*,R*) form of the ring-opened hydroxy-acid having the structure shown above. *See* col. 13, line 51. The "(R*,R*)"

stereochemical designation necessarily refers to a racemic mixture of ring-opened heptanoic acids that contains two mirror-images, or "enantiomers." The structures of each of the R*, R* stereoisomers in this, so-called "trans"-form racemic mixture, as disclosed in Example 1, are as follows:



R-(R*, R*) enantiomer



S-(R*, R*) enantiomer

By convention, the designation "(R*, R*)" refers to a racemic mixture that contains both the "R,R" and "S,S" stereoisomers, as shown above. Also, the designation R-(R*, R*) refers to the specific enantiomer shown on the left, above, in which the *absolute* stereochemistry for the two hydroxyl groups is (R, R). Likewise, S-(R*, R*) refers to the enantiomer shown on the right above in which the absolute stereochemistry for the two hydroxyl groups is (S,S). The claims of the '995 Patent recite the R-(R*, R*) stereoisomer.

Example 1 of the '893 Patent thus discloses a racemic mixture containing the R-(R*, R*) enantiomer (as claimed in the '995 Patent) and the S-(R*, R*) enantiomer. The '893 Patent does not expressly disclose a method for separating these enantiomers from one another.

The '893 Patent also discloses that two other stereoisomers (total of four) exist for the disclosed lactones:

> The compounds of structural formula I above possess two asymmetric carbon centers, one at the 4-hydroxy position of the pyran-2-one ring, and the other at the 6-position of the pyran-2-one ring where the alkylpyrrole group is attached. This asymmetry gives rise to four possible isomers, two of which are the R-cis- and S-cis-isomers and the other two of which are the R-trans- and S-trans-isomers. This invention contemplates only the trans- form of the compounds of formula I above.

'893 Patent at col. 3, lines 45-54. The '893 Patent also discloses the four stereoisomers for the corresponding ring-opened heptanoic acid.

The '893 Patent also discloses certain "pharmaceutically acceptable metal salts" of the preferred trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide, including the "sodium, potassium, calcium, magnesium, aluminum, iron, and zinc" salts. *See* '893 Patent, col. 7, lines 8-10. The '893 Patent also generally discloses pharmaceutically acceptable amine salts of trans-5-(4-

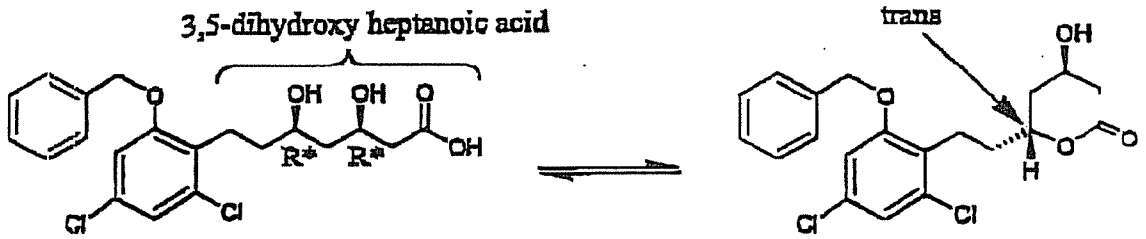
fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide and explains that in describing such salts, it "contemplates salts with ammonium and organic nitrogenous bases strong enough to form salts with carboxylic acids." *See* '893 Patent, col. 7, lines 10-13.

Furthermore, the '893 Patent disclosed (and generically claimed) "a pharmaceutical composition for treating hypercholesterolemia comprising a hypocholesterolemic effective amount of" the trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide and a pharmaceutically acceptable carrier. *See* '893 Patent, Claim 8. The '893 Patent also disclosed (and generically claimed) "a method of inhibiting cholesterol synthesis in a human suffering from hypercholesterolemia comprising administering" the trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide in unit dosage form. *See* '893 Patent, Claim 9.

2. United States Patent No. 4,375,475 – The '475 Patent

U.S. Patent No. 4,375,475 ("the '475 Patent") issued on March 1, 1983 and thus is prior art to the '995 Patent under 35 U.S.C. §102(b); it was published more than one year prior to July 21, 1989, the earliest date to which the '995 patent could conceivably claim domestic priority. We note that the '475 Patent was cited in the '893 Patent, and was itself prior art to the '893 Patent under 35 U.S.C. §102(b), and was cited by applicants in that patent.

The '475 Patent generally discloses lactones and corresponding dihydroxy acids which are said to be hypocholesterolemic and hypolipemic. Example 14 describes the lactone (±) trans-6-[2-(2,4-dichloro-6-phenylmethoxyphenyl)ethyl]-3,4,5,6-tetrahydro-4-hydroxy-2H-pyran-2-one and the corresponding ring-opened hydroxy-acid having the following chemical structures:



Ring-opened hydroxy-acid

Lactone

The lactones and dihydroxy acids described in Example 14 share the trans and R*,R* stereochemical configurations, respectively, with the lactones and the dihydroxy acids of the '893 and '995 patents. The '475 Patent expressly teaches that the "trans" form of the lactone is preferred, and that the ring-opened heptanoic acid contains two enantiomers of this "trans" form. *See* '475 Patent, col. 4, lines 1-43. The '475 also discloses that the "4 R enantiomers," having

the (R,R) absolute conformation "specifically inhibit with high potency the activity of 3-hydroxy-3-methylglutaryl-coenzyme A reductase [HMG-CoA reductase], which is known to be the enzyme involved in the rate limiting step in the process of cholesterol biosynthesis." *Id.* This reference also indicates that the "(+) trans enantiomer" is a preferred compound of this invention. *Id.* at col 4, lines 34-43. Indeed, in the Background of the Invention section, the '475 Patent also notes that the naturally occurring cholesterol biosynthesis inhibitor compactin, having this absolute conformation, "was reported by Brown et al., *J. Chem. Soc. Perkin I*, 1165 (1976)." (*See* '475 Patent, at 1:46-52.)

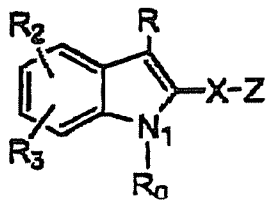
To obtain this particular enantiomer from the "trans" racemate, the '475 Patent discloses a method for separating (or "resolving") the two enantiomers in Example 14. *See* '475 Patent, col. 28, line 32-col. 29, line 23. This method involves an initial step of reacting the trans-lactone with a particular enantiomer of methylbenzylamine to form a diastereomeric mixture of dihydroxy amides. These diastereomers are then separated by a conventional chromatographic technique, *see* '475 Patent, col. 12, lines 3-14, and the methylbenzylamine moiety cleaved to yield the separate enantiomers.

Thus, the '475 patent shows that, at the time the '995 patent was filed, those skilled in the art recognized that derivatives of 3,5-dihydroxy heptanoic acid existed in the form of racemic mixtures, that those racemic mixtures could be separated into their component enantiomers, and that there was a preference for the (R,R) absolute conformation of the 3,5-dihydroxy heptanoic acid corresponding to the stereochemistry of the naturally occurring cholesterol biosynthesis inhibitor compactin.

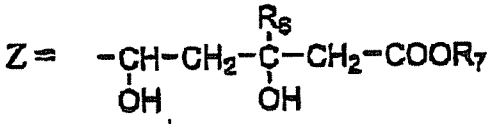
3. United States Patent No. 4,739,073 – The '073 Patent

U.S. Patent No. 4,739,073 ("the '073 Patent") issued on April 19, 1988 and thus is prior art to the '995 Patent under 35 U.S.C. §102(b); it was published more than one year prior to July 21, 1989, the earliest date to which the '995 patent could conceivably claim domestic priority.

The '073 Patent, like the '893 and '475 Patents, discloses lactones and corresponding dihydroxy acids useful for inhibiting cholesterol biosynthesis. *See generally* '073 Patent, Abstract. For example, the '073 Patent discloses the following structure:



See col. 1, lines 15-20. This structure represents a 3,5-dihydroxy heptanoic acid derivative when X is a $-CH_2-CH_2-$ group as described at column 1, lines 58-59 and Z is the following group, as described at column 1, lines 63-68:



where Z, R_6 and R_7 are hydrogen as described at col. 2, lines 10-12. The '073 Patent also specifically recognizes the existence of the four stereoisomeric forms of this structure, which are referred to in the '073 Patent as the (R,R); (R,S); (S,R); and (S,S) enantiomers. *See* '073 Patent at col. 2, line 65 - col. 3, line 9. The designations "(R,R)" and "R-(R*, R*)" (see discussion of '893 patent, *supra*) refer to the same absolute stereoisomeric configuration.

For such structures, the '073 specifically states that the (R,R) absolute configuration is preferred:

> The preferred stereoisomers of the compounds of Formula I wherein X is -$(CH_2)_m$-, and Z is a group of Formula II are the 3R,5R and 3R,5S isomers and the racemate of which each is a constituent, i.e., the 3R,5R-3S,5S (erythro) and 3R,5S-3S,5R (threo) racemates, with the 3R,5R isomer and the racemate of which it is a constituent being more preferred and *the 3R,5R isomer being most preferred.*

Id. at col. 5, lines 28-35 (emphasis added). In reading this passage, those skilled in the art would have recognized that the numerals "3" and "5" in the term "3R,5R" designated the positions of the carbon atoms to which the hydroxyl groups are attached.

Thus, the '073 patent would have taught those of skill in the art that, at the time the '995 patent was filed, that 3,5-dihydroxy heptanoic acid derivative existed in four stereochemical forms and that the R,R enantiomer was the most preferred.

C. The Claims of the '995 Patent are Obvious in View of the Prior Art

As explained above, an analysis of obviousness first requires a determination of the differences between the subject matter sought to be patented and the prior art, if any, and an analysis to determine if those differences are such that the subject matter of the claim, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art. The trier of fact would be required to determine the scope and content of the prior art. Based on such findings and the court's determination of the scope and meaning of the claimed invention, the court will make a legal determination regarding whether the differences between the prior art and the claim would have been obvious to one having ordinary skill in the art at time the claimed the invention was made. As explained below, a court properly applying the law would determine that any difference between the subject matter of each claim of the '995 Patent, viewed as a whole, and the prior art would have been obvious.

1. The Scope and Content of the Prior Art

The prior art, at the time of filing the application for the '995 Patent, disclosed at least the following:

The racemic mixture of the trans-6-[2-(3- or 4-carboxamido-substituted pyrrol-1-yl)alkyl]-4-hydroxypyran-2-ones (and the racemic mixture of the corresponding heptanoic acid), having the (R*,R*) relative conformation, as disclosed in the '893 Patent, was an active cholesterol biosynthesis inhibitor. This trans lactone was known to exist as a racemic mixture. (*See* '893 Patent).

Pharmaceutically acceptable metal salts of trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide were known, including sodium, potassium, calcium, magnesium, aluminum, iron, and zinc salts. (*See* '893 Patent).

Pharmaceutically acceptable amine salts of trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide were known, including salts with ammonium and organic nitrogenous bases strong enough to form salts with carboxylic acids. (*See* '893 Patent).

Pharmaceutical compositions were known for treating hypercholesterolemia comprising a hypocholesterolemic effective amount of the trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide and a pharmaceutically acceptable carrier. (*See* '893 Patent).

Methods were known for inhibiting cholesterol synthesis in humans suffering from hypercholesterolemia by administering the trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide in unit dosage form. (*See* '893 Patent).

The absolute (R,R) conformation on the heptanoic acid moiety, as known to exist in the naturally occurring cholesterol biosynthesis inhibitor compactin, was known to be the preferred conformation for inhibition of cholesterol biosynthesis. (*See* '475 and '073 Patents).

A motivation existed in the art to separate (or "resolve") the (R,R) enantiomer of the "trans" racemic mixture to yield the (R,R) enantiomer in a form essentially free of the (S,S) enantiomer, as well as to use the enantiomer to provide a pharmaceutical composition for treating hypercholesterolemia. (*See* '475 and '073 Patents).

A generalized method was known for the separation (or "resolution") of racemic mixtures of the trans-heptanoic acid analogues of compactin, to yield the (R,R) and (S,S) absolute conformations essentially free of the alternate enantiomer. *See* '475 Patent.

2. Claim-By-Claim Analysis Of Prima Facie Obviousness

Each of the claims of the '995 Patent is *prima facie* obvious:

Claim 1 of the '995 Patent refers to the absolute R-(R*,R*) heptanoic acid form and the 2R-trans lactone form of the racemic "trans" atorvastatin disclosed in the '893 Patent. Thus, the only difference between the subject matter of this claim and the express disclosure of the '893 Patent lies in the fact that this claim is directed to the R-enantiomers. A court would construe this claim as referring to the respective R-enantiomers essentially free of the respective S-enantiomers.

However, the difference between these "purified" R-enantiomers and the racemic mixtures of the '893 Patent would have been obvious. First, as disclosed by the '475 and '073 Patents, the absolute (R,R) conformation on the heptanoic acid moiety was known to be the preferred absolute conformation for inhibition of cholesterol biosynthesis, as this conformation was known to exist in the naturally occurring cholesterol biosynthesis inhibitor compactin. Second, there existed a generalized teaching regarding a method to resolve the enantiomers in a racemic mixture of heptanoic acids of the '893 Patent. As in the *Adamson* case, discussed above, the bare knowledge that the racemate of the '893 Patent existed, in combination with a generalized method of separating the enantiomers from the '475 Patent provided ample motivation to separate the racemate of the primary reference. Therefore a court would conclude that Roth, by using the precise separation method disclosed in the '475 Patent to resolve the racemic mixture of the '893 Patent, merely followed "the teachings of the ['475 Patent] prior art [and did] no more than the obvious." *In re Adamson*, 275 F.2d at 954-955.

Claim 2 of the '995 Patent, drawn specifically to the heptanoic acid form of the enantiomer of Claim 1, would also be found by a court to be *prima facie* obvious. As noted above, the lactone and heptanoic acid forms of the enantiomers of Claim 1 were known to be readily interconverted.

Claim 3 of the '995 Patent, drawn to the lactone form of the enantiomer of Claim 1, is also *prima facie* obvious. As noted above, the lactone and heptanoic acid forms of the enantiomers of Claim 1 were known to be readily interconverted.

Claim 4 of the '995 Patent, drawn to the monosodium salt would have been *prima facie* obvious. The prior art '893 Patent disclosed various pharmaceutically acceptable metal salts of the trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide, including the sodium, potassium, calcium, magnesium, aluminum, iron, and zinc salts.

Claim 5 of the '995 Patent, drawn to the monopotassium salt would have been similarly *prima facie* obvious.

Claim 6 of the '995 Patent, drawn to the hemicalcium salt would have been similarly *prima facie* obvious.

Claim 7 of the '995 Patent, drawn to the N-methylglucamine salt, a standard, well-known and readily available amine salt, would have been *prima facie* obvious. The prior art '893 Patent disclosed various pharmaceutically acceptable *amine* salts of trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide, including salts with ammonium and organic nitrogenous bases strong enough to form salts with carboxylic acids.

Claim 8 of the '995 Patent, drawn to the hemimagnesium salt would have been *prima facie* obvious, for reasons similar to those presented for claims 4-6.

Claim 9 of the '995 Patent, drawn to the hemizinc salt, would have been similarly *prima facie* obvious.

Claim 10 of the '995 Patent, drawn to a mixture with 1-deoxy-1-(methylamino)-D-glucitol, a standard, well-known and readily available amine derivative of sorbitol in admixture with the heptanoic acid form of the enantiomer of Claim 1, would have also been *prima facie* obvious, for reasons similar to those presented for claim 7.[6]

Claim 11 of the '995 Patent, drawn to a pharmaceutical composition for treating hypercholesterolemia comprising an effective amount of either the lactone or the heptanoic acid form of the enantiomer of Claim 1, is also *prima facie* obvious. The prior art '893 Patent discloses pharmaceutical compositions for treating hypercholesterolemia comprising a hypocholesterolemic effective amount of the trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide and a pharmaceutically acceptable carrier. The substitution of the purified enantiomer in place of the racemic mixture in such a composition would have been obvious.

Claim 12 of the '995 Patent, drawn to a method of inhibiting cholesterol synthesis in a human suffering from hypercholesterolemia by administering an effective amount of either the lactone or the heptanoic acid form of the enantiomer of Claim 1, is also *prima facie* obvious.

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[6] As Ranbaxy's proposed formulation does not include a mixture of any atorvastatin with a 1-deoxy-1-(methylamino)-D-glucitol, Ranbaxy, additionally, does not infringe this claim of the '995 Patent.

The prior art '893 Patent discloses methods for inhibiting cholesterol synthesis in humans suffering from hypercholesterolemia by administering the trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide in unit dosage form. The substitution of the purified enantiomer in place of the racemic mixture in such a composition would have been obvious.

3. Objective Indicia of Alleged Nonobviousness

Based on the foregoing analysis, a court would conclude that each claim of the '995 Patent is *prima facie* obvious. A court would then consider any relevant indicia of non-obviousness introduced by the patentee in an effort to rebut a *prima facie* case of obvious, although it would ultimately disregard any such evidence if the *prima facie* case of obviousness is strong and the express teachings of the prior art come "within a hairsbreadth of anticipation." *SIBIA Neurosciences*, 225 F.3d at 1359. A court properly applying the law would not be persuaded by the evidence of record.

a. Comparison Of IC_{50} Values For Racemate And Purified R-(R*,R*) Enantiomer Does Not Support A Finding Of Unexpected Results

The '995 Patent states that it provides:

> compounds consisting of [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-((1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic acid (*compound of formula I*), pharmaceutically acceptable salts thereof and (2R-trans)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide (the lactone form of the heptanoic acid or *compound of formula II*).

('995 patent at 2:29-38; emphasis added). The '995 Patent also states, in comparing these specific formulae and compounds:

> The compounds according to the present invention and especially according to the compound of the *formula I* inhibit the biosynthesis of cholesterol as found in the CSI screen that is disclosed in U.S. Pat. No. 4,681,893 which is now also incorporated by reference therefor. The CSI data of the *compound I*, its enantiomer the *compound II* and the racemate of these two compounds are as follows:

Compound	IC_{50} (micromoles/liter)
[R-(R*R*)] isomer	0.0044
[S-(R*R*)] isomer	0.44
Racemate	0.045

> Accordingly, the present invention is the pharmaceutical composition prepared from the compound of the *formula I or II* or pharmaceutically acceptable salts thereof.

('995 patent at 7:65 – 9:10). This data shows activity of the S-enantiomer:racemate:R-enantiomer in the ratios of roughly 1:10:100. It appears that the data from this CSI cholesterol biosynthesis inhibition study presented in the '995 Patent may have been obtained using the heptanoic acid form of the purified [R-(R*R*)] enantiomer of atorvastatin, and the lactone form of the purified [S-(R*R*)] enantiomer of atorvastatin. There is no indication concerning what form, heptanoic acid or lactone, of the racemate atorvastatin was used.

The '893 patent describes the CSI screen as follows:

> The ability of compounds of the present invention to inhibit the biosynthesis of cholesterol was measured by two methods. A first method (designated CSI screen) utilized the procedure described by R. E. Dugan et al., *Archiv. Biochem. Biophys.*, (1972), 152, 21-27. In this method, the level of HMG-CoA enzyme activity in standard laboratory rats is increased by feeding the rats a chow diet containing 5% cholestyramine for four days, after which the rats are sacrificed.
>
> The rat livers are homogenized, and the incorporation of cholesterol-^{14}C-acetate into nonsaponifiable lipid by the rat liver homogenate is measured. The micromolar concentration of compound required for 50% inhibition of sterol synthesis over a one-hour period is measured, and expressed as an IC_{50} value.

(The '893 Patent at 7:38 - 8:4).

It is our understanding that, in addition to numerous enzymes necessary to convert ^{14}C-acetate to cholesterol, the supernatant also includes various other enzymes and, more importantly, various endogenous inhibitors of cholesterol biosynthesis, some of which may even act as inhibitors specific to the HMG-CoA reductase enzyme. A researcher of ordinary skill in the art at the time of the filing of the '187 Application would not have considered the crude CSI assay described by the '995 Patent and Roth to provide reliable kinetic data due to the existence of numerous endogenous enzymes and inhibitors.

Thus, based on the uncertainty regarding whether the heptanoic acid or lactone forms were used in the specific assay, and based on the myriad and varied interactions that the two enantiomeric inhibitors could experience in the supernatant used for the CSI screen employed, one skilled in the art would not have considered the IC_{50} data presented in the '995 Patent to be unexpected.

In the course of prosecuting the '995 Patent, the named inventor, Roth, submitted a declaration under 37 C.F.R. § 1.132 on February 25, 1991. In this declaration, Roth specifically

alleged that the hemicalcium salt of the heptanoic acid-form of R-(R*,R*) atorvastatin[7] exhibited unexpected activity, based upon the following data.

Compound	IC_{50} (micromoles/liter)
[R-(R*R*)] isomer	0.025
[S-(R*R*)] isomer	>1.00
Racemate	0.26

Although Roth states that the inhibitors were assessed using essentially the CSI screen that is disclosed in U.S. Patent No. 4,681,893, he provides no explanation for the almost two-fold difference between the values reported in his declaration and the values reported in the '995 Patent, or for the nearly ten-fold difference between the values reported in his declaration and the values reported in the '893 Patent for the lactone-form "trans" racemate of atorvastatin: IC_{50} = 0.035 micromoles/liter. Moreover, while the relative activities reported in the declaration for S-enantiomer:racemate:R-enantiomer may still be approximately 1:10:100, as in the '995 Patent data, Roth does not provide a precise value for the IC_{50} of the S-enantiomer.

Specifically, in his declaration, Roth alleged that "the data demonstrate that the Compound I [the purified R-(R*R*) enantiomer] provides an IC50 which indicates activity greater than fifty-fold more than that of Compound II [the purified S-(R*R*) enantiomer] and which indicates activity at least ten-fold more than that of the racemate." *See* Roth Declaration, ¶ 9. Roth further alleged that "the differences in the data ... among Compounds I, II and racemate shows that activity of Compound I is surprising and unexpected *because if the Compound II is accepted as inactive*, the activity of the Compound I would be expected to be only accepted as twice that of the racemic mixture." *See* Roth Declaration, ¶ 10 (emphasis added).

Thus, Roth expressly based his *expectation* that the R-enantiomer would be two-fold as active as the racemate on an *assumption*: that the S-enantiomer is inactive. However, Roth does not provide any reasoning or analytic support for the assumption that the S-enantiomer would be inactive in the above-described CSI screen. Indeed, there was ample reason for an artisan of ordinary skill, at the time of filing, to believe that both enantiomers would be active, if at different levels, in such a crude screen. Moreover, as noted above, the prior art teaches that that the R-enantiomer form of the heptanoic acid, corresponding to the stereochemistry of the naturally-occurring cholesterol biosynthesis inhibitors mevinolin and compactinin, is the desirable enantiomer and is preferable to the S-enantiomer. However, no prior art of which we are aware suggests that the S-enantiomer would be wholly inactive as a cholesterol biosynthesis inhibitor, especially in the context of the crude CSI screen. Rather, an artisan of ordinary skill, at the time of filing, would have simply expected that the S-enantiomer would be less active than the R-enantiomer.

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7 It is therefore apparent that each enantiomer and the racemate of the Roth declaration were tested as the hemicalcium salt of the heptanoic acid form of atorvastatin.

Furthermore, the assumption upon which Roth based his conclusion of "unexpected results" is *contradicted* by the data provided in the '995 Patent, itself. Specifically, the data presented in the '995 Patent clearly shows that purified S-(R*,R*) atorvastatin is *active* as an inhibitor under the CSI screen; purified S-(R*,R*) atorvastatin is shown to be approximately ten-fold less active than the racemate. The data in Roth's declaration, unlike that in the '995 Patent, show the IC_{50} for the S-enantiomer as merely ">1.0," suggesting that the IC_{50} may be quite high and, therefore, that its activity may be quite low. However, the parallel data in the '995 Patent indicates that the IC_{50} of the S-enantiomer is only ten-fold greater than that of the racemate and, therefore, that the S-enantiomer is only approximately ten-fold less active than the racemate. Such data is inconsistent with an assumption that the S-enantiomer is inactive. Accordingly, it appears that Roth advanced a counter-factual assumption: that the S-enantiomer was inactive. That the IC_{50} data were inconsistent with this assumption should not be considered "surprising and unexpected," because the assumption itself was known to be incorrect.

Accordingly, a court properly applying the law would conclude that each claim of the '995 Patent is obvious in view of the prior art, and that the "evidence" presented by Roth during the prosecution of the '995 Patent is unpersuasive in showing non-obviousness in view of the strong prime facie case of obviousness.

Summary

Accordingly, the drug product for which RLL is seeking approval to market in ANDA No. 76-477 does not infringe any valid claim of the '995 patent.

Very truly yours,

for Jay R. Deshmukh
Vice President – Intellectual Property

CIVIL COVER SHEET

The JS 44 civil cover sheet and the information contained herein neither replace nor supplement the filing and service of pleadings or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the docket sheet. (SEE INSTRUCTIONS ON THE REVERSE OF THE FORM.)

I. (a) PLAINTIFFS
PFIZER INC, PFIZER IRELAND PHARMACEUTICALS, WARNER-LAMBERT COMPANY, WARNER-LAMBERT COMPANY, LLC and WARNER-LAMBERT EXPORT, LTD.

(b) County Of Residence of First Listed Plaintiff _____
(EXCEPT IN U.S. PLAINTIFF CASES)

(c) ATTORNEYS (FIRM NAME, ADDRESS AND TELEPHONE NUMBER)
Rudolf E. Hutz (#484)
CONNOLLY BOVE LODGE & HUTZ LLP
1007 N. Orange Street, P.O. Box 2207
Wilmington, Delaware 19899 Telephone: (302) 658-9141

DEFENDANTS
RANBAXY LABORATORIES LIMITED, RANBAXY INC. and Ranbaxy Pharmaceuticals, Inc.

County Of Residence Of First Listed Defendant: _____
(IN U.S. PLAINTIFF CASES ONLY)

NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE LAND INVOLVED.

ATTORNEYS (IF KNOWN)

II. BASIS OF JURISDICTION (Place an "X" In One Box Only)

- ☐ 1 U.S. Government Plaintiff
- ☒ 3 Federal Question (U.S. Government Not a Party)
- ☐ 2 U.S. Government Defendant
- ☐ 4 Diversity (Indicate Citizenship of Parties in Item III)

III. CITIZENSHIP OF PRINCIPAL PARTIES (Place an "X" In One Box for Plaintiff and One Box for Defendant)
(For Diversity Cases Only)

	PTF	DEF		PTF	DEF
Citizen of This State	☒ 1	☐ 1	Incorporated *or* Principal Place of Business In This State	☐ 4	☐ 4
Citizen of Another State	☐ 2	☐ 2	Incorporated *and* Principal Place of Business in Another State	☐ 5	☐ 5
Citizen or Subject of a Foreign Country	☐ 3	☐ 3	Foreign Nation	☐ 6	☐ 6

IV. NATURE OF SUIT (Place an "X" In One Box Only)

CONTRACT
- ☐ 110 Insurance
- ☐ 120 Marine
- ☐ 130 Miller Act
- ☐ 140 Negotiable Instrument
- ☐ 150 Recovery of Overpayment & Enforcement of Judgment
- ☐ 151 Medicare Act
- ☐ 152 Recovery of Defaulted Student Loans (Excl Veterans)
- ☐ 153 Recovery of Overpayment of Veteran's Benefits
- ☐ 160 Stockholders Suits
- ☐ 190 Other Contract
- ☐ 195 Contract Product Liability
- ☐ 196 Franchise

REAL PROPERTY
- ☐ 210 Land Condemnation
- ☐ 220 Foreclosure
- ☐ 230 Rent Lease & Ejectment
- ☐ 240 Torts to Land
- ☐ 245 Tort Product Liability
- ☐ 290 All Other Real Property

TORTS

PERSONAL INJURY
- ☐ 310 Airplane
- ☐ 315 Airplane Product Liability
- ☐ 320 Assault. Libel & Slander
- ☐ 330 Federal Employers Liability
- ☐ 340 Marine
- ☐ 345 Marine Product Liability
- ☐ 350 Motor Vehicle
- ☐ 355 Motor Vehicle Product Liability
- ☐ 360 Other Personal Injury

PERSONAL INJURY
- ☐ 362 Personal Injury - Med. Malpractice
- ☐ 365 Personal Injury - Product Liability
- ☐ 368 Asbestos Personal Injury Product Liability

PERSONAL PROPERTY
- ☐ 370 Other Fraud
- ☐ 371 Truth in Lending
- ☐ 380 Other Personal Property Damage
- ☐ 385 Property Damage Product Liability

CIVIL RIGHTS
- ☐ 441 Voting
- ☐ 442 Employment
- ☐ 443 Housing/ Accommodations
- ☐ 444 Welfare
- ☐ 445 Amer. w/Disabilities – Employment
- ☐ 446 Amer. w/Disabilities – Other
- ☐ 440 Other Civil Rights

PRISONER PETITIONS
- ☐ 510 Motions to Vacate Sentence

HABEAS CORPUS:
- ☐ 530 General
- ☐ 535 Death Penalty
- ☐ 540 Mandamus & Other
- ☐ 550 Civil Rights
- ☐ 555 Prison Condition

FORFEITURE/PENALTY
- ☐ 610 Agriculture
- ☐ 620 Other Food & Drug
- ☐ 625 Drug Related Seizure of Property 21 USC 881
- ☐ 630 Liquor Laws
- ☐ 640 R.R. & Truck
- ☐ 650 Airline Regs.
- ☐ 660 Occupational Safety/Health
- ☐ 690 Other

LABOR
- ☐ 710 Fair Labor Standards Act
- ☐ 720 Labor/Mgmt Relations
- ☐ 730 Labor/Mgmt Reporting & Disclosure Act
- ☐ 740 Railway Labor Act
- ☐ 790 Other Labor Litigation
- ☐ 791 Empl. Ret. Inc. Security Act

BANKRUPTCY
- ☐ 422 Appeal 28 USC 158
- ☐ 423 Withdrawal 28 USC 157

PROPERTY RIGHTS
- ☐ 820 Copyrights
- ☒ 830 Patent
- ☐ 840 Trademark

SOCIAL SECURITY
- ☐ 861 HIA (1395ff)
- ☐ 862 Black Lung (923)
- ☐ 863 DIWC/DIWW (405(g))
- ☐ 864 SSID Title XVI
- ☐ 865 RSI (405(g))

FEDERAL TAX SUITS
- ☐ 870 Taxes (U.S. Plaintiff or Defendant)
- ☐ 871 IRS - Third Party 26 USC 7609

OTHER STATUTES
- ☐ 400 State Reapportionment
- ☐ 410 Antitrust
- ☐ 430 Banks and Banking
- ☐ 450 Commerce
- ☐ 460 Deportation
- ☐ 470 Racketeer Influenced ar Corrupt Organizations
- ☐ 480 Consumer Credit
- ☐ 490 Cable/Sat TV
- ☐ 810 Selective Service
- ☐ 850 Securities/ Commodities Exchange
- ☐ 875 Customer Challenge 12 USC 3410.
- ☐ 890 Other Statutory Actions
- ☐ 891 Agricultural Acts
- ☐ 892 Economic Stabilization Act
- ☐ 893 Environmental Matters
- ☐ 894 Energy Allocation Act
- ☐ 895 Freedom of Information Act
- ☐ 900 Appeal of Fee Determination Under Equal Access to Justice
- ☐ 950 Constitutionality of State Statutes

V. ORIGIN (PLACE AN "X" IN ONE BOX ONLY)

☒ 1 Original Proceeding ☐ 2 Removed from State Court ☐ 3 Remanded from Appellate Court ☐ 4 Reinstated or Reopened ☐ 5 Transferred from another district (specify) ☐ 6 Multidistrict Litigation ☐ 7 Appeal to District Judge from Magistrate Judgment

VI. CAUSE OF ACTION
Cite the U.S. Civil Statute under which you are filing **(Do not cite jurisdictional statutes unless diversity):**
35 U.S.C. § 271
Brief description of cause:
Patent infringement.

VII. REQUESTED IN COMPLAINT: ☐ CHECK IF THIS IS A CLASS ACTION UNDER F.R.C.P. 23 **DEMAND:** CHECK YES only if demanded in complaint: **JURY DEMAND:** ☐ YES ☒ NO

VIII. RELATED CASE(S) IF ANY (See instructions): JUDGE DOCKET NUMBER
Pfizer Inc. et al. v. Ranbaxy, Farnan, J., Civil Action No. 03-209-JJF; Pfizer Inc. et al. v. Ranbaxy, Farnan, J., Civil Action No. 07-138-JJF; Pfizer Inc. et al. v. Teva Pharmaceuticals. Inc., Civil Action No. 07-360-JJF; Pfizer Inc. et al. v. Cobalt Pharmaceuticals, Inc., Civil Action No. 07-790-JJF .

DATE SIGNATURE OF ATTORNEY OF RECORD

3/24/2008 /s/Rudolf E. Hutz (#484)

FOR OFFICE USE ONLY

RECEIPT # AMOUNT APPLYING IFP JUDGE MAG. JUDGE

INSTRUCTIONS FOR ATTORNEYS COMPLETING CIVIL COVER SHEET FORM JS–44

Authority For Civil Cover Sheet

The JS–44 civil cover sheet and the information contained herein neither replaces nor supplements the filings and service of pleading or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. Consequently, a civil cover sheet is submitted to the Clerk of Court for each civil complaint filed. The attorney filing a case should complete the form as follows:

I. **(a) Plaintiffs – Defendants.** Enter names (last, first, middle initial) of plaintiff and defendant. If the plaintiff or defendant is a government agency, use only the full name or standard abbreviations. If the plaintiff or defendant is an official within a government agency, identify first the agency and then the official, giving both name and title.

(b) County of Residence. For each civil case filed, except U.S. plaintiff cases, enter the name of the county where the first listed plaintiff resides at the time of filing. In U.S. plaintiff cases, enter the name of the county in which the first listed defendant resides at the time of filing. (NOTE: In land condemnation cases, the county of residence of the "defendant" is the location of the tract of land involved.)

(c) Attorneys. Enter the firm name, address, telephone number, and attorney of record. If there are several attorneys, list them on an attachment, noting in this section "(see attachment)".

II. **Jurisdiction.** The basis of jurisdiction is set forth under Rule 8(a), F.R.C.P., which requires that jurisdictions be shown in pleadings. Place an "X" in one of the boxes. If there is more than one basis of jurisdiction, precedence is given in the order shown below.

United States plaintiff. (1) Jurisdiction based on 28 U.S.C. 1345 and 1348. Suits by agencies and officers of the United States are included here.

United States defendant. (2) When the plaintiff is suing the United States, its officers or agencies, place an "X" in this box.

Federal question. (3) This refers to suits under 28 U.S.C. 1331, where jurisdiction arises under the Constitution of the United States, an amendment to the Constitution, an act of Congress or a treaty of the United States. In cases where the U.S. is a party, the U.S. plaintiff or defendant code takes precedence, and box 1 or 2 should be marked.

Diversity of citizenship. (4) This refers to suits under 28 U.S.C. 1332, where parties are citizens of different states. When Box 4 is checked, the citizenship of the different parties must be checked. (See Section III below: federal question actions take precedence over diversity cases.)

III. **Residence (citizenship) of Principal Parties.** This section of the JS 44 is to be completed if diversity of citizenship was indicated above. Mark this section for each principal party.

IV. **Nature of Suit.** Place an "X" in the appropriate box. If the nature of suit cannot be determined, be sure the cause of action, in Section VI below, is sufficient to enable the deputy clerk or the statistical clerks in the Administrative Office to determine the nature of suit. If the cause fits more than one nature of suit, select the most definitive.

V. **Origin.** Place an "X" in one of the seven boxes.

Original Proceedings. (1) Cases which originate in the United States district courts.

Removed from State Court. (2) Proceedings initiated in state courts may be removed to the district courts under Title 28 U.S.C. Section 1441. When the petition for removal is granted, check this box.

Remanded from Appellate Court. (3) Check this box for cases remanded to the district court for further action. Use the date of remand as the filing date.

Reinstated or Reopened. (4) Check this box for cases reinstated or reopened in the district court. Use the reopening date as the filing date.

Transferred from Another District. (5) For cases transferred under Title 28 U.S.C. Section 1404(a). Do not use this for within district transfers or multidistrict litigation transfers.

Multidistrict Litigation. (6) Check this box when a multidistrict case is transferred into the district under authority of Title 28 U.S.C. Section 1407. When this box is checked, do not check (5) above.

Appeal to District Judge from Magistrate Judgment. (7) Check this box for an appeal from a magistrate judge's decision.

VI. **Cause of Action.** Report the civil statute directly related to the cause of action and give a brief description of the cause. **Do not cite jurisdictional statues unless diversity.** Example: U.S. Civil Statute: 47 USC 553
Brief Description: Unauthorized reception of cable service.

VII. **Requested in Complaint.** Class Action. Place an "X" in this box if you are filing a class action under Rule 23, F.R.Cv.P.

Demand. In this space enter the dollar amount (in thousands of dollars) being demanded or indicate other demand such as a preliminary injunction.

Jury Demand. Check the appropriate box to indicate whether or not a jury is being demanded.

VIII. **Related Cases.** This section of the JS 44 is used to reference related pending cases if any. If there are related pending cases, insert the docket numbers and the corresponding judge names for such cases.

Date and Attorney Signature. Date and sign the civil cover sheet.